FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF CINNARIZINE USING DIFFERENT SUPERDISINTEGRANTS

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In partial fulfillment of the requirement for the

award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted By

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Under the guidance of

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled, **"*FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLET OF CINNARIZINE USING DIFFERENT SUPERDISINTEGRANTS*.** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai was carried out by **Mr. MANE SUBHASH NAMDEO,** Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 for the partial fulfilment for the award of degree of Master of Pharmacy in Pharmaceutics under my supervision.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

Place: Erode

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EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled "***FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF CINNARIZINE USING DIFFERENT SUPERDISINTEGRANTS.*****"** submitted to the Tamil Nadu Dr. M.G.R. Medical University Chennai, was carried out by **Mr. MANE SUBHASH NAMDEO** in the department of pharmaceutics, Nandha College of Pharmacy, Erode-52 in the partial fulfilment of the degree of "Master of Pharmacy" in pharmaceutics under supervision of **Dr. S. Tamizharasi, M.Pharm., Ph.D.** HOD.. Pharmaceutics department, Nandha College of Pharmacy, Erode-52.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

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DECLARATION

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The work presented in this thesis entitled **"*FORMULATION AND EAVALUATION OF ORAL DISPERSIBLE TABLETS OF CINNARIZINE USING DIFFERENT SUPERDISINTEGRANTS.*"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 under the direct supervision **Dr. S. Tamizharasi, M.Pharm., Ph.D.** HOD. Pharmaceutis, Nandha College of Pharmacy, Erode-52.

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ABBREVIATIONS

Abbreviations	Abbreviation Terminology
ODT	Oral dispersible tablet
FDT	Fast dissolving/dispersible tablets
BP	British Pharmacopoeia
MMC	Micro crystalline cellulose
SSG	Sodium starch glycolate
SLS	Sodium lauryl sulphate
cm	Centimeter
C	Celsius
Conc.	Concentration
CR	Controlled release
Fig	Figure
FTIR	Fourier transform infra red
GIT	Gastro intestinal tract
Gm	Gram
g/cm^2	Gram per square centimeter
Hrs	Hours
H	Hour
HCL	Hydrochloric acid
pH	Hydrogen ion concentration
IP	Indian Pharmacopoeia
Kg	Kilogram
LBD	Loose bulk density
#	Mesh size
µg	Microgram
mg	Milligram
ml	Milliliter
min	Minutes
nm	Nanometer
%	Percentage
RS	Reference standard
RH	Relative humidity
±	Standard Deviation
TBD	Tapped bulk density
t	Time
USP	United State Pharmacopoeia

Dedicated
To
My Loving Parents,
And
Research Guide

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1. INTRODUCTION;[1,2]

The drug administration from oral route have wide acceptance up to 50-60% of total dosage forms. The solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for the some patients, is difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

Oral dispersible tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapimelts, porous tablets, quick dissolving etc. Oral dispersible tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of oral dissolving dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European pharmacopoeia adopted the term " Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.

According to **European pharmacopoeia,** the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of ODT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), cellactose80, sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva.

The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing of the oral dispersing tablets are freeze-drying, spray-drying, tablet moulding, sublimation, sugar-based excipients, tablet compression and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

Recent developments in technology have presented viable alternatives for the patients who may have difficulty in swallowing tablets or liquids. Traditional tablets and capsules administered with an 8-oz, the glass of water may be inconvenient or impractical for some patients. For example a very elderly patient may not be able to swallow a daily dose of antihistaminic drugs. An eight year old child with allergies could use a more convenient dosage form than antihistamine syrup. A schizophrenic patient the institution setting can hide a conventional tablet under his or her tongue to avoid their daily of dose of atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her h_2-blockers.

To overcome these drawbacks, orally dispersible tablets (ODT) or mouth dissolving tablet (MDT); has emerged as alternative oral dosage forms. These are novel types, of tablets that disintegrate/dissolve/disperse in saliva within few seconds.

1.A) TABLETS :[3]

Tablets may be defined as solid pharmaceutical dosage forms containing medicament or medicaments with or without suitable recipients & prepared either by compression or molding.

i) Advantages of tablets:

Some of the potential advantages of tablets are as follows.

- They are the unit dosage form having greatest capabilities amongst all the oral dosage form for the dose precision and least content variability.
- Their cost is lowest amongst all the oral dosage forms.
- They are lightest and the most compact amongst all the oral dosage form.
- They are easiest and cheapest for packaging and transportation.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- Tablets are better suited to large-scale production than other unit oral dosage forms.
- They have the best-combined properties of chemical, mechanical, microbiological stability amongst all the oral dosage forms.

ii) Classification of tablets:

Based on the route of administration or the function, the tablets are classified as follows.

1) Tablets ingested orally.

- Compressed tablet
- Multiple compressed tablet
    - i) Layered Tablet
    - ii) Compression coated Tablet
- Repeat action Tablet
- Delayed action and enteric-coated Tablet
- Sugar and chocolate-coated tablet
    - a) Film coated tablet
    - b) Chewable Tablet

2) Tablets used in the oral cavity.

- Buccal Tablet
- Sublingual Tablet
- Troches and Lozenges
- Dental cones

3) Tablets administered by other routes.

- Implantation Tablet
- Vaginal Tablets

4) Tablets used to prepare solution.

- Effervescent Tablet
- Dispensing Tablet
- Hypodermic Tablet
- Tablets Triturates

iii) Manufacturing Methods [3]

Tablets are manufactured by Direct compression, Wet granulation or Dry granulation method.

1) Direct Compression:

The term direct compression is used to define the process by which tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity & forms a firm compact.

2) Wet Granulation:

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets.

3) Dry Granulation:

In this technique, there is no use of liquids. The process involves the formation of slugs. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

Table No.1.1: The processing Steps Commonly required in the Various Tablet preparation techniques:

Processing steps	Wet Granulation	Dry Granulation	Direct Compression
Raw materials	✓	✓	✓
Weight	✓	✓	✓
Screen	✓	✓	✓
Mix	✓	✓	-
Compress (slug)	-	✓	-
Wet mass	✓	-	-
Mill	✓	-	-
Dry	✓	-	-
Mill	✓	✓	-
Mix	✓	✓	-
Compress	✓	✓	✓

iv) Advantages of Direct compression :-

- This process is more economical. It requires fewer manufacturing steps, less processing time & thus reduces labour cost & less process validation.
- The processing steps required no need of moisture, heat, and high compaction pressure.
- There is an optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass & is available for dissolution.

In the present aging society, easy-to-use dosage forms for elderly patient, whose swallowing function is often decreased, are in great demand. The use of conventional tablets, capsules, and liquid or syrup preparations were not always easy-to-use dosage forms for elderly patients because of their decrease motor function. Similarly the use of conventional tablets is challenging to paediatric, geriatric, and uncooperative patients who may have difficulty to

swallow tablets and is also problematic when water is unavailable or when patients have a persistent cough or gag-reflux.

These problems have been addressed by the recent introduction of Oral dispersible tablets(ODT) which also known as a quick-dissolving tablet (also known as fast-dissolving, fast-dissolving multiparticulate, rapid-dissolving, mouth-dissolving, fast-melting, fast dispersing tablets) is an oral tablets that does not require water for swallowing. The tablets dissolve within 60 seconds when placed in mouth or in oral cavity.

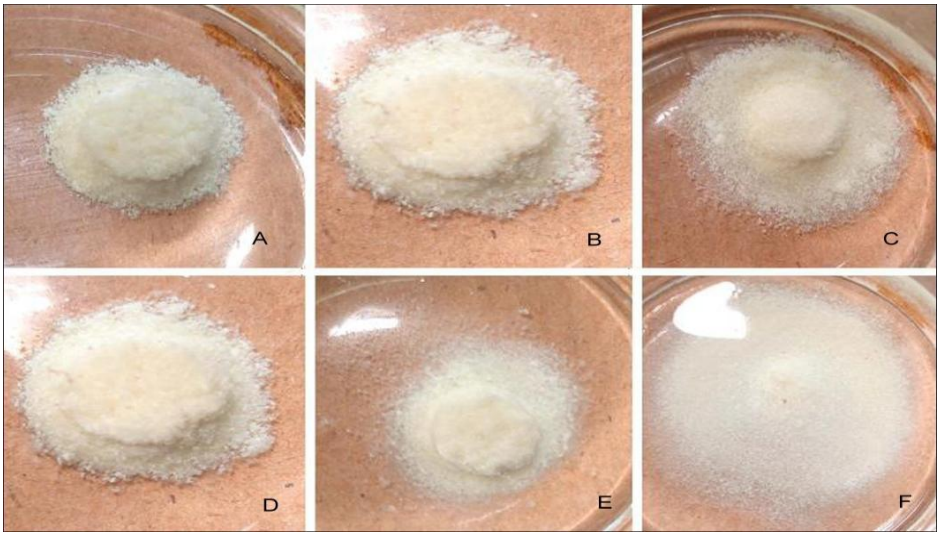
1.B) ORAL DISPERSIBLE / DISINTEGRATING TABLET[4]

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the dosage form developed to facilitate ease of medication, the oral dispersible tablet is one of the most widely employed commercial products.

i) Defination

A oral-dissolving drug delivery system in most cases is a tablet that dissolving or disintegrates in the oral cavity without the need of water or chewing. Most oral-dissolving drug delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patients saliva along with the soluble and insoluble excipients.

These are also called melt-in-mouth, repimelt, porous tablet, fast dissolving, quick dissolving or rapid disintegrating tablets. Oral Disintegrating tablets are also called as Oro-dispersible tablets, Quick disintegrating tablets , Fast disintegrating tablets, rapid dissolving tablets and Rapimelts.



A **B** **C**

Figure 1.1: A- Disintegration of Oro dispersible tablet after 5 seconds

B- Disintegration of Oro dispersible tablet after 10 seconds

C- Disintegration of Oro dispersible tablet after 15 seconds

D- Disintegration of Oro dispersible tablet after 20 seconds

E- Disintegration of Oro dispersible tablet after 25 seconds

F- Disintegration of Oro dispersible tablet after 30 seconds

Recently, **European Pharmacopoeia** has used the term Oro-dispersible tablets that disperses readily and within 3 min in mouth before swallowing.

United State Food and Drug Administration (FDA) defined Oro-dispersible tablets as, "A solid dosage form containing medicinal substance of active ingredient which disintegrates usually within a matter of seconds."

"Oral dispersible tablets is solid dosage form that contains medicinal substances And that disintegrate and dissolve rapidly without water (within seconds) ."

The need for delivering drugs to patients efficiently and with few side effects has prompted pharmaceutical companies to engage in the development of the new drug delivery

systems. A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as oral dispersing dosage form or oral dissolving tablets. When this type of tablet is gone into the stomach, the 0.1N HCL will serve to rapidly dissolve the tablet.

Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. The target populations for these new oral-dissolving/disintegrating dosage forms have generally been pediatric, geriatric, bedridden or developmentally disabled patients., who are traveling or who have little or no access of water are also good candidates for oral dissolving / disintegrating tablets. Other groups that may experience problems using conventional oral dosage form include the mentally ill, developmentally disable and patients who are uncooperative. A difficulty in swallowing (dysphasia) tablets or capsules is common problem among all age groups, especially in elderly and pediatrics. For this reasons, tablets that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention.

Indeed, Oral dispersible tablet is an important and attractive alternative to liquid dosage form. Syrups are best for pediatrics but they are bulky and drugs are not as stable in liquid form as in solid form like tablets.

Oro-dispersible tablets are characterized by high porosity, and low hardness, when administered an in-situ suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true oral-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed oral-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. the disintegration time of these tablets depend largely on size and hardness parameters.

ii) Criteria for Oral dispersible Drug Delivery System [(2)]

- The tablets should not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant the mouth feel.
- Leave minimum or no residue in mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging
- Equipments at low cost.

iii) Requirements of oral dispersible tablets;

An ideal ODT should

- Require no water for oral administration, yet dissolving/disperse/disintegrate in a matter of seconds.
- Be harder and less friable.
- Leave minimal or on residue in mouth after administration.
- Exhibit low sensitivity to environment condition (temperature and humidity).
- Allow the manufacture of tablet by using conventional processing and packing equipment.

iv) Advantages of ODT;

- Ease of administration to patient who refuse to swallow a tablet, such as paediatric, geriatric, and psychiatric patient.
- Convenience of administration and accurate dosing as compared to liquid.
- No need of water to swallow the dosage form, which is highly convenient feature for patient who are travelling and do not have immediate access to water.
- Good mouth feels property of ODT helps to change the basic view of medication as "bitter pill" particularly for paediatric patients.
- Rapid dissolution of drug and absorption, which may produce rapid, onset of action.

- Some drug are absorbed from the mouth and oesophagus as the saliva passes down into the stomach in such cases bioavailability of drug is increased.
- Ability to provide advantage of liquid medication in the form of solid preparation.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved bioavailability and as a result of reduced dosage improved clinical performance through a reduction of unwanted effect.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drug from mouth, pharynx and oesophagus as saliva passes down.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

v) Disadvantages of ODT;

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated Properly.
- Tablets are very fragile and lack physical resistance. Because the tablets are very porous and low compression forces are used to prepare them. They cannot be packed in conventional strips or in bottles and special packaging is required.
- Bitter drugs have to be taste masked by various techniques which in turn increases the time and cost of production.

Their growing importance of oral dispersible tablet was under lined recently when European Pharmacopoeia adopted the term "Oro-dispersible Tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.

vi) Salient feature of Oral Dispersible Drug Delivery System;

- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Quick disintegration and dissolution of the dosage form.
- Overcomes unacceptable taste of the drugs.

- Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery

vii) Possible benefits of orally dispersible drugs.

1. Clinical:

- Improved drug absorption.
- Faster onset of action.
- Minimized first pass effect.
- Improved bioavailability.

2. Medicinal:

- No tablet or capsule to swallow or chew.
- Better taste, no water needed.
- Improved safety and efficacy.
- Improved compliance.

3. Technical:

- More accurate dosing than liquid products.
- Can use sugars and other excipients that are generally recognized as safe.
- Improved stability because of unit-dose packaging.
- Manufactured with common process and conventional equipment.

4. Business:

- Lifecycle Management: re-formulation is a strategy to prolong market exclusivity as it may delay or reduce generic erosion at patent expiry.
- Differentiation in a crowded market
- For generic companies it offer the prospect of superior generic drugs in order to gain market dominance upon the expiration of patents
- Cost effective drug development

1.3) Mechanism of tablet disintegrates [1]

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

1. Capillary action
2. Swelling
3. Because of heat of wetting
4. Disintegrating particle/particle repulsive forces
5. Deformation
6. Release of gases
7. Enzymatic action

1) Capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrates maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

2) Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

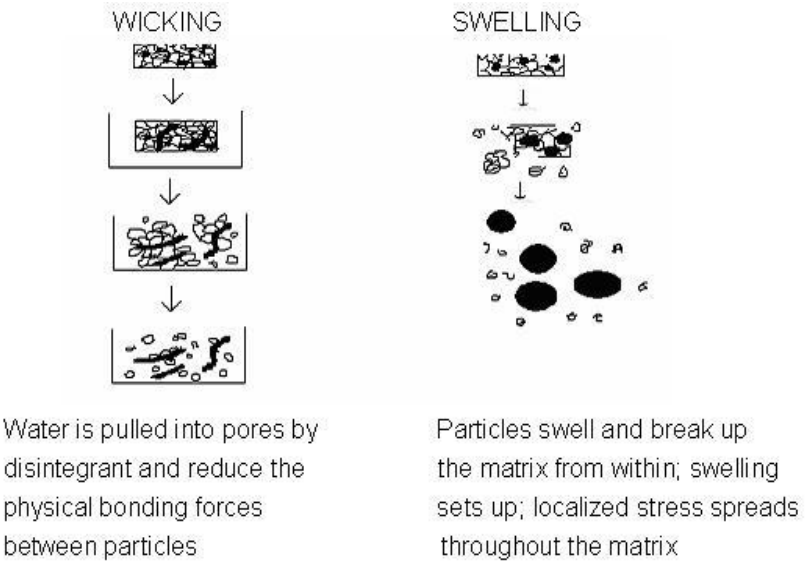


Fig.no.1.2 : Disintegration of tablet by wicking and swelling

3) Heat of wetting (air expansion)

When disintegrates with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrates and cannot describe the action of most modern disintegrating agents.

4.) Disintegrating particle / particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrates. Guyot-Hermann has proposed a particle repulsion theory based On the observation that non-swelling particle also cause disintegration of tablet. The electric Repulsive force between particle are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

5.) Deformation.

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when

granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet.

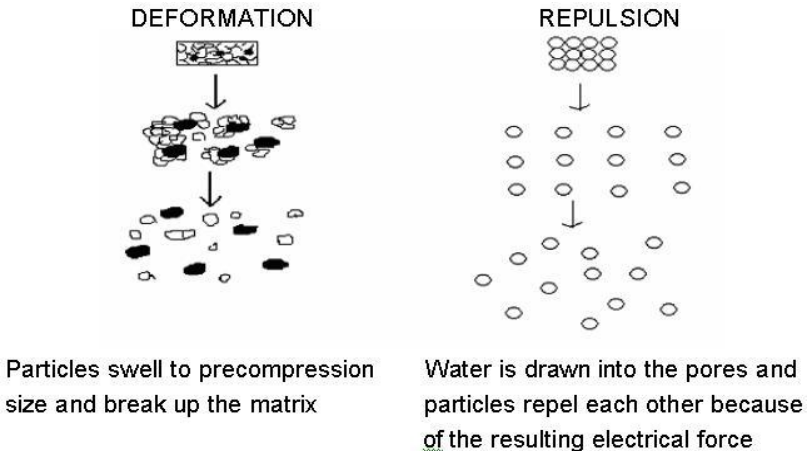


Fig.1. 3. Disintegration by deformation and repulsion

6) Release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrates are highly sensitive to small changes in humidity level and temperature ,strict control of environment is required during manufacturing of the tablets .The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

7) Enzymatic reaction

Here, enzymes presents in the body act as disintegrates. These enzymes destroy the binding action of binder and helps in disintegration.

Table.1.2. Disintegrating Enzymes.

ENZYMES	BINDER
Amylase	Starch
Protease	Gelatin
Cellulose	Cellulose and its derivatives
Invertase	Sucrose

ix) Fundamentals of oral dispersible tablets:

For rapid dissolution or disintegration of dosage form, water must rapidly penetrate into the tablet matrix to cause quick disintegration & instantaneous dissolution of the tablet. Several techniques are used to achieve these fundamentals, to formulate mouth-dissolving tablet. Some of the techniques are described below.

1.4) Techniques for Preparing Oral Dispersible Tablets [(5)]

Many techniques have been reported for the formulation of Orodispersible tablets.

1. Freeze drying / lyophilisation
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

1. Freeze-Drying or Lyophilisation

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The

mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophilisation technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2. Tablet Moulding:

Moulding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. The mechanical strength of moulded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilisation technique, tablets produced by the moulding technique are easier to scale up for industrial manufacture.

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is moulded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Moulded tablets have a porous structure

that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet.

To overcome poor taste masking characteristic Van Scoik. Incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form. Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on whether and to what extent it dissolves in the wetted mass. The drug can exist as discrete particles or micro particles in the matrix. Different moulding techniques can be used to prepare mouth-dissolving tablets:

a. Compression Moulding: The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

b. Heat Moulding: A molten matrix in which drug is dissolved or dispersed can be directly moulded into orodispersable Tablets.

c. No vacuum lyophilization: This process involves evaporation of solvent from a drug solution or suspention at a standard pressure.

Moulded tablets possess porous structure, which facilitates rapid disintegration and easy dissolution. Moulded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But moulded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength

3. Spray Drying:

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium

bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4. Sublimation:

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalicanhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane;benzene can be used as pore forming agents.

The basis of this technique is to add inert solid ingredients that volatilize readily, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.

Koizumi et al applied the sublimation technique to prepare highly porous compressed tablets that were rapidly soluble in saliva. Mannitol and camphor were used as a tablet matrix material and subliming the material respectively. Camphor was iminated by subliming in vacuum at 80 ^{0}C for 30 minutes to develop pores in the tablets.

Makino et al described a method of producing a fast dissolving tablet using water as a pore forming material. A mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc) were moistened with water (1- 3 %w/w) and compressed into tablets. The water was then removed yielding highly porous tablet that exhibited excellent ;

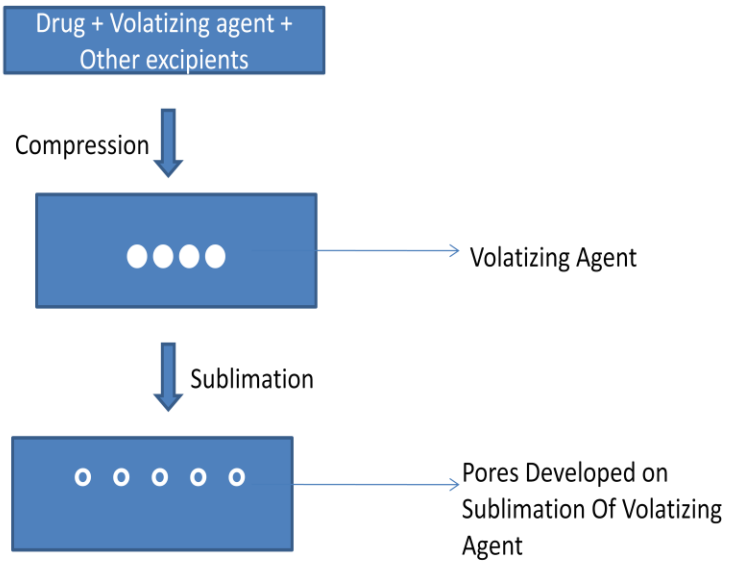


Fig No 1. 4 Steps involved in Sublimation Technology

5. Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing

mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

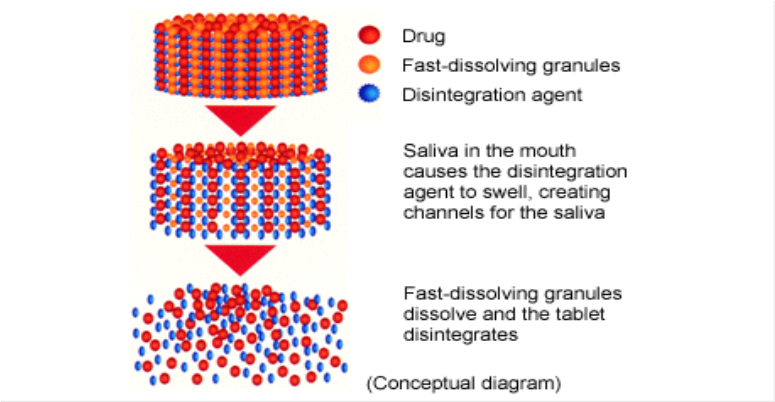


Fig. No1.5 Compression of Sugar Based Excipients

6. Mass-Extrusion:

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and there by achieve taste masking.

2. REVIEW OF LITERATURE

Adimoolan Senthil *et al* 2010[10] Flunarizine HCL mouth dissolving tablets have been developed at 40-mg dose, with the intention off facilitating administration to patients experiencing problems with swallowing and hopefully, improving its poor oral bioavailability.

Avani R Gosai *et al*[53] Preparation, physicochemical characterization, dissolution and formulation studies of ondacetron cyclodextrin inclusion complexes The objective of this research was to prepare, characterize, and to study dissolution properties of inclusion complexes of ondacetron, with *β*-cyclodextrin and hydroxypropyl-*β*-cyclodextrin and to study effect of complexation on aqueous solubility and rate of dissolution in dissolution media. The highest improvement in solubility and *in-vitro* drug release were observed in inclusion complex prepared with HP-*β*-CD by kneading method. Improvement in solubility and *in-vitro* drug release of ondacetron was more with HP-*β*-CD as compared to *β*-CD

Sudhir Bhardwaj *et al* (2010)[15] Formulation and evaluation of fast dissolving tablet of aceclofenac. Aceclofenac (anti-inflammatory and analgesic) was selected as the model drug. The poor aqueous solubility of the drug results in variable dissolution rate and hence poor bioavailability. It was concluded that the fast dissolving tablets of poor soluble drug can be made by direct compression technique using selective super disintegrates showing enhanced dissolution, taste masking and hence better patient compliance and effective therapy.

R Margret chandira *et al* 2010[8] formulation and evaluation of mouth dissolving tablets of the etoricoxib. Etoricoxib is a new non-steroidal anti-inflammatory drug (NSAID) the main criteria for mouth dissolving tablets are to disintegrate or dissolve rapidly in oral cavity with saliva in 15sec to 60sec with need of water. the disintegrants used should fulfill the criteria by the disintegrating the tablets in specified time limit in the present investigation variety of super disintegrants like primogel, kollidone, ac-di-sol, l-hpmc, l-hpc, were selected and tablets were prepared by direct compression method in different concentration like 4% and 8%.

Rakesh Pahwa *et al* 2010[1] studies of Orally Disintegrating Tablets - Friendly to Pediatrics and Geriatrics to obviate the problem of dysphagia and to improve patient compliance, ODTs have gained considerable attention as preferred alternatives to conventional tablet and capsule formulations these the techniques render the disintegration of tablet rapidly and dissolve in mouth without chewing or additional water intake.

Akbari B.V. *et al* (2010) [6] studies on formulation and in vitro evaluation of fast dissolving tablets of domperidone the formulations containing croscarmellose sodium, cross povidone, L-HPC and cellactose80 as superdisintegrants, disintegrated faster compared to the formulation containing microcrystalline cellulose. in vitro drug release showed that almost drug was release in the range of 94-97% range in 10 minutes. Depending upon cumulative drug release, in vitro disintegration time, wetting time, there was found that direct compression method is better than wet granulation method.

Indhumathi D *et al* (2010) [11]study of design and optimization of orodissolving tablet of antidepressant drug by the superdisintegrants addition method mouth dissolving tablet offers a solution for pediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance *in vitro* dissolution studies show the release is in the following order of superdisintegrants: crospovidone > pregelatinized starch > croscarmellose > sodium starch glyacolate. Maximum *in vitro* dissolution was found to be with formulation f-7 and it clearly shows due to crospovidone (4%), this is also confirmed by *in vivo* pharmacokinetic studies.

Debjit Bhowmik *et al* (2009)[2] carried out the Fast Dissolving Tablet: An Overview Fast dissolving Tablets are disintegrating and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. In some cases such as motion sickness, sudden episodes of allergic attack or coughing, and an unavailability of water, swallowing conventional tablets may be difficult.

Nitesh Patel *et al* (2011)[5] performed Design and Characterization of Oral Dispersible Tablet of Ciinarizine. Cinnarizine is an Anti-histamine drug which is insoluble in water; hence the drug may be slowly or incompletely dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore its bioavailability is less) In the present study an attempt has been made to prepare Oral Dispersible tablets of Cinnarizine by using Superdisintegrants–Crospovidone, Ac-de-sol, Sodium starch glycolate, level of addition to increase the rate of drug release from dosage form to increase the dissolution rate by adding surfactant SLS and hence its bioavailability. The Disintegration time of Fast Dissolving tablets were increased by the addition of concentration of Superdisintegrants.

Raguia Ali Shoukri *et al* (2009)[12] had study on vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets development of a lyophilized orally disintegrating tablet (ODT) that enhanced the in vitro dissolution and in vivo absorption of nimesulide, a drug with poor solubility and poor bioavailability is presented.

C.P. JAIN *et al* 2009[13] Carried out the formulation and evaluation of fast dissolving tablets of Valsartan. In this investigation the fast dissolving tablets of Valsartan were prepared using different Superdisintegrants by direct compression method. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. The release of Valsartan from FDTs was found to follow non-Fickian diffusion kinetics.

Bhupendra G Prajapati *et al* (2009) [7] A Review on Recent patents on Fast Dissolving Drug Delivery System. A allergic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antihistamine. Fast-dissolving/disintegrating tablets (FDDTs) are a perfect fit for all of these patients. FDDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and

are more appropriately termed fast disintegrating tablets, as they may take up to a minute to completely disintegrate

D.Nagendrakumar *et al* (2010)[22] have prepared Orodispersible tablets of ganisetron using various concentrations of the superdisintegrant agents like Ac-Di-Sol, crospovidone, sodium starch glycolate by direct compression method.

Uddhav Bagul *et al* (2010)[45] Reported formulation of Orodispersible capsules containing a soluble complex of the drug with beta-cyclodextrin. This work aimed to improve levocetrizine bioavailability by formulating it in Orodispersible capsules containing a soluble complex of the drug with beta-cyclodextrin. The Complexes were prepared by different methods and characterized by differential scanning calorimetry, X-ray diffraction, infrared spectroscopy and dissolution efficiency studies. Orodispersible capsule shells were prepared from conventional hard gelatin capsule shells by freeze-drying and evaluated by image analysis microscopy and moisture content estimation. Formulae containing the freeze-dried complex and different fillers were prepared and characterized for their flowability, moisture content and moisture absorption behavior. The Orodispersible capsules were evaluated *in-vitro* and *in-vivo* in comparison with levocetrizine commercial tablets (Levosiz).

Vasanthakumar Sekar *et al* 2008[16] In the present study an attempt has been made to prepare the immediate release tablets of telmisartan by using Polyplasdone XL-10 (Crospovidone) at intragranular, extragranular and partly intra and extragranular level of addition to increase the rate of drug release from dosage form to increase the dissolution rate and hence its bioavailability. The prepared granules and tablets were evaluated for their physiochemical properties and *invitro* dissolution study was conducted for the prepared tablets. It was concluded that the immediate release tablets with proper hardness, disintegration time and with increase rate of dissolution can be made using Polyplasdone XL-10

Avani F. Amin (2006)[18] Emerging Trends In The Development Of Orally Disintegrating Tablet Technology new formulation trend is emerging and gaining popularity because it is easy administration and leads to better patient compliance. These dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and release the drug as soon as they come in contact with the saliva, thus obviating the need for water during administration.

G. Abdelbar *et al* (2005)[19] determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration the assessment of the in vitro disintegration profile of rapidly disintegrating tablets (RDT) is very important in the evaluation and the development of new formulations of this type. so far neither the us pharmacopoeia nor the European pharmacopoeia has defined a specific disintegration test for rdt; currently, it is only possible to refer to the tests on dispersible or effervescent tablets for the evaluation of rdt's disintegration capacity. The obtained time–distance profiles or disintegration profiles enabled the calculation of certain quantitative values as the disintegration onset ($t1$) and the total disintegration time ($t2$). These values were used in the characterization of the effect of test variables as the disintegration medium and temperature on the disintegration time of RDT.

P. S. Zade *et al* (2009)[30] have formulated fast dispersible tablets which disintegrated either rapidly in water to form a stabilized suspension or disperse instantaneously in the mouth to be swallowed without the aid of water. They employed a rotatable central composite design to predict the effects of the quantitative factors, mannitol and cross-povidone as well as compression force on the characteristics of tablet.

Wolfgang Wienen *et al* 2000[21] A Reviews on Telmisartan Novel, Long-Acting Angiotensin II-Receptor Antagonist Telmisartan is a potent, long-lasting, nonpeptide antagonist of the Angiotensin II type-1 (AT1) receptor that is indicated for the treatment of essential hypertension. Telmisartan is not a prodrug and has a longer terminal elimination half-life than other commercially available sartans (24hrs), making it suitable for once-daily dosing. In animal models, telmisartan exhibits pronounced cardioand reno-protective effects in animals with severe, essential hypertension. In clinical studies, telmisartan shows comparable antihypertensive

activity to members of other major antihypertensive classes, such as ACE inhibitors, beta blockers and calcium antagonists. These trials have confirmed the placebo-like safety and tolerability of telmisartan in hypertensive patients. Based on these data, telmisartan offers advantages over other sartans and represents an important new treatment option for hypertension.

UK Drug Information Pharmacists Group (2000)[22] new medicines on the market of antihistaminic drugs.

DP Venkatesh *et al*[24].the Formulation of taste masked oro-dispersible tablets of Ambroxol hydrochloride Ambroxol hydrochloride (HCL) is a potent mucolytic capable of inducing bronchial secretion Thus, in the work under taken, an attempt was made to mask the taste and to formulate into a oro-dispersible tablet by the complexation with ion exchange resins, which also acts as super disintegrating agents. Since, these tablets can be swallowed in the form of dispersion, it is suitable dosage form for pediatric and geriatric patients. Cation exchange resins like Indion-204 and Indion-234 were utilized for the sorption of drug. Drug-resinates was prepared in drug to resin ratio of 1:5 and 1:6. Also, the dispersion not showing any bitter taste, indicate the capability of ion exchange resins used, both as taste masking and super disintegrating agents

Yourong Fu, *et al*[27] Developments, Technologies, Taste-Masking and Clinical Studies Upon introduction into the mouth, these tablets were dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. Th is review describes various formulations and tech nologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity In particular; this review describes in detail FDT technologies based on lyophilization, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spraydrying, moisture treatment, sintering, and use of sugar-based disintegrants.

NG Raghavendra Rao *et al* [23] study on development of carbamazepine fast dissolving tablets: effect of functionality of hydrophillic carriers on solid dispersion technique An attempt has been

made for the development of fast dissolving tablets of the carbamazepine by solid dispersion methods, using different concentrations of croscarmellose sodium as super disintegrating agent and study the effect of various carriers on solid dispersion technique. The major problem of this drug is very low solubility in biological fluids and poor bioavailability after oral administration. The results concluded that fast dissolving tablets of poorly soluble drug, carbamazepine showing enhanced dissolution will lead to improved the bioavailability, improved the effectiveness and hence better patient compliance.

3. AIM AND SCOPE

Before carrying out the study, its need should be clearly defined, such that the study present itself as a valuable contribution to the field of study as well as a thoughtful investment of the researcher's time.

The aim is to study is to develop and evaluate the oral dispersible tablet of Cinnarizine.

- To enhanced the onset of action of Cinnarizine.
- To enhance the solubility by using surfactant.
- To prepared and cost effective direct compression methods.

The main aim is to increase the disintegration time by using the different super-disintegrants and to increase solubility of the cinnarizine drug by using surfactant. The present work is concerned with the formulation and characterization of cinnarizine orodispersable tablets for oral administration. Different drug compatible excipients were tried as filler and binder and the objective is to increase the release rate of dissolution by increase the release rate of drug from the solid oral dosage form by using different superdisintegrants.

Cinnarizine bioavailability is near about 42% so it is benefit of once daily administration. The cinnarizine absorb from both i.e. oral cavity and gastro cavity. Half Life Bi-exponential decay kinetics with a terminal elimination half-life of approximately 3-4 hours The daily dose of cinnarizine for treatment of nausea and vomiting is minimum 25mg for adults for the management of histamine disorders, adult initially and for children dose greater than 12 years 25 mg and for 6 to 12 years 25mg dose twise a daily.

The objective of present work is to mask the taste of cinnarizine by using aspartame and menthol with physical mixture method and to develop the oral dispersible drug delivery system by simple and cost effective method. Scope of this dosage form is more comfortable for the patients who are suffering from dysphagia, the bedridden and the clinical condition where water intake is limited.

The main objective is to develope oral dispersible tablets and provides the patients complains product.

- To develop a physicochemical stable drug delivery system of cinnarizine.
- To evaluate all the parameters of formulation in details including stability study.

4. PLAN OF WORK

1. **Literature survey;**

2. **Prefromulation studies;**

   I) Identification and Characterization of Cinnarizine.

   - Melting point.
   - Infrared absorption spectrophotometer.

   .

   II) Development of standard calibration curve of Cinnarizine.

3. **Formulation Design;**

   - Development of oral dispersible tablet formulation using Three different super disintegrating agent.
   - Preparation of powder blend of drug and excipients
   - Preparation of oral dispersible tablet of cinnarizine by direct compression.

4. **Assessment of powder blend;**

   - Angle of repose
   - Bulk density
   - Tapped density
   - Compressibility index
   - Hausner ratio

5. **Compression of powder blend into tablet by direct compression method;**

6. **Post compression assessment of oro-dispersible tablets;**

   - Weight variation
   - Hardness
   - Friability
   - Thickness
   - Wetting time

- Water absorption ratio
- *In-vitro* disintegration
- *In-vitro* dissolution

7. Stability studies;

8. Comparison of Best Formulation with all batches;

9. Result and discussion;

10. Summary and conclusion;

5. DRUG PROFILE

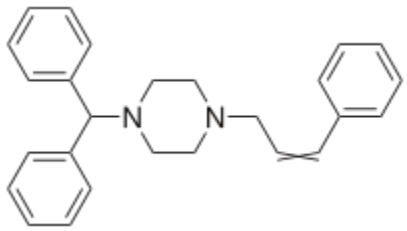
Cinnarizine [24]

Chemical Formula: $C_{26}H_{28}N_2$

Chemical Name: 1-trans-cinnamyl-4-diphenylmethyl-piperazine.

IUPAC Name: 1-(diphenylmethyl)-4-(3-phenylprop-2-en-1-yl)piperazine.

Chemical Structure:



Drug Category: Antihistamine (H_1 – antagonist), calcium channel blocker.

Molecular Weight: 368.514 g/mol

State: Solid

Melting Point: 118-122^{0}C

Solubility: Soluble in ethanol or DMSO

Indication: For the treatment of motion sickness,vomiting and vertigo.

Dose: Minimum 25mg to Maximum 75mg

pKa: 1.95,7.5

Mechanism of Action:

Cinnarizine inhibits contraction of vascular smooth muscle cell by blocking L-Type and T-Type voltage gated calcium channels. Cinnarizine has also been implicated in binding to dopamine D_2 receptor, histamine H_1 receptor, and muscarnic acetylcholin receptor.

Pharmacodynamics:

Cinnarizine inhibits contractions of vascular smooth muscle cells by blocking calcium channels. Cinnarizine increases erythrocyte deformability and decreases blood viscosity in vitro. Cinnarizine inhibits stimulation of the vestibular system

Absorption:

Cinnarizine is well absorbed from the gastrointestinal tract. The pharmacokinetics of a single oral dose in healthy volunteers have been studied. Peak plasma concentrations in fasting subject are seen at 1- 3 h following administration of 75 mg cinnarizine, and are not significantly affected by the formulation of the drug. The plasma half-life is 3.04±0.83 h (mean ± SD).

Disrtibution:

Cinnarizine is widely and rapidly distributed throughout body tissues, as would be expected for a highly lipid soluble drug. There is rapid absorption of the administered compound from the GI tract and peak tissue levels occur within 1 hour, except in the gonads where the peak is reached only after 4-8h. For the liver, the peak level corresponded to 6% of the administered dose and for all other tissues (i.e., brain, heart, lung, spleen, kidneys) it was less than 0.5%. Plasma protein binding of cinnarizine is 91%.

Metabolism and Excreation:

Cinnarizine undergoes a number of biotransformations, which include N-oxidation, C-oxidation, and oxidative cleavage of the drug. It undergoes metabolism and has a half-life of 3 to 4 hours after oral administration. Human data on the metabolism and excretion of cinnarizine are limited but suggest that cinnarizine undergoes extensive metabolism.

. Unchanged drug was found only in very small quantities in the urine, but more variable amounts were found in the feces. The major urinary metabolites are cinnarizine-n-oxide and benzhydrol and major fecal metabolites are benzhydrylpiperazine and p-hydroxybenzophenone.

Dosage and administration:

The recommended dose for treatment of vestibular symptoms in adult and children over 12 years is 30mg three times daily. For children from 5-12 years half the dose is recommended i.e., 15 mg three times daily.

For prophylaxis of motion sickness, 75 mg for adults and Children from 5-12 years should take half the adult dose.

Drug Interactions:

Cinnarizine may potentiate the effect of antidepressant and alcohol. Antacid medicines and H_2 blocker, accelerates resorption of preparation, reducing acidity of the stomach fluid. Nootrope agent and vasodilators increase cinnarizine effect.

Adverse reactions:

Cinnarizine may potentiate the effect of antidepressant and alcohol. Antacid medicines and H_2 blockers accelerates resorption of preparations, reducing acidity of stomach fluid.Nootrope agent and vasodilators increase cinnarizine effect.

Contraindications:

In patients with known hypersensitivity to cinnarizine. Patients with a diagnosis of parkinson's disease should not be given cinnarizine. Cinnarizine should be used with caution in hypotensive patients. The safety of cinnarizine tablets in pregnant and lactating women has not been established.

Storage:

Store in cool and dry place,

Away from direct heat and light.

6. Superdisintegrant Profile

A) Crosspovidone

IUPAC name: Polyvinylpyrollidone

Synonym: PVP, Povidone, PolyvidonePoly [1-(2-oxo-1-pyrrolidinyl) ethylene] 1-Ethenyl-2-pyrrolidon homopolymer 1-Vinyl-2-pyrrolidinon-Polymere Copovidone PNVP.

Molecular formula: $(C_6H_9NO)_n$

Molar mass: 2.500 - 2.5000.000 $g \cdot mol^{-1}$

Appearance: white to light yellow, hygroscopic, amorphous powder.

Density: 1.22 gm/cm³

Melting point: 110 - 180 °C (glass temperature),

Solubility: Completely insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic. Swells rapidly in water. Rapidly disperses in water, but Does not gel even after prolonged exposure.

Physical Characteristics: pH (10% slurry): 5.0 – 8.0 Moisture (Karl-Fisher): £ 5.0%

Table. No. 6.1

Product	Typical Average Particle size (microns)	Tap Density (g/cc)	Bulk Density (g/cc)
Polyplasdone XL	100	0.3	0.2
Polyplasdone XL-10	30	0.5	0.3
Polyplasdone INF-10	11	0.5	0.4

Properties PVP is soluble in water and other polar solvents. When dry it is a light flaky powder, which readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

Uses

The monomer is extremely toxic to aquatic life.

1. **Medical**

The polymer PVP was used as a blood plasma expander for trauma victims after the first half of the 20th century. It is used as a binder in many pharmaceutical tablets; it simply passes through the body when taken orally. However, autopsies have found that crospovidone does contribute to pulmonary vascular injury in substance abusers who have injected pharmaceutical tablets intended for oral consumption. The long-term effects of crospovidone within the lung are unknown. PVP added to iodine forms a complex called povidone-iodine that possesses disinfectant properties. This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs. It is known for instance under the trade name Betadine.

2. **Technical**

PVP is also used in many technical applications:

- As adhesive in glue stick and hot melts
- As special additive for batteries, ceramics, fibreglass, inks, inkjet paper and in the chemical-mechanical planarization process
- As emulsifier and disintegrant for solution polymerization
- As photoresist for cathode ray tubes (CRT)
- use in aqueous metal quenching
- for production of membranes, such as dialysis and water purification filters
- As a binder and complexation agent in agro applications such as crop protection, seed treatment and coating
- As a thickening agent in tooth whitening gels

- As an aid for increasing the solubility of drugs in liquid and semi-liquid dosage forms (syrups, soft gelatine capsules) and as an inhibitor of recrystallisation
- As an additive to Doro's RNA extraction buffer

3. Other uses

PVP is also used in personal care products, such as shampoos and toothpastes, in paints, and adhesives that must be moistened, such as old-style postage stamps and envelopes. It has also been used in contact lens solutions and in steel-quenching solutions. PVP is the basis of the early formulas for hair sprays and hair gels, and still continues to be a component of some. As a food additive, PVP is a stabilizer and has E number**E1201**. PVPP is **E1202**. It is also used in the wine industry as a fining agent for white wine. Other references state that polyvinyl pyrrolidone and its derivatives are fully from mineral synthetic origin. Therefore, its use in the production should not be a problem for vegans.

In molecular biology, PVP can be used as a blocking agent during Southern blot analysis as a component of Denhardt's buffer. It is also exceptionally good at absorbing polyphenols during DNA purification. Polyphenols are common in many plant tissues and can deactivate proteins if not removed and therefore inhibit many downstream reactions like PCR.

Safety

The USFDA has approved this chemical for many uses and it is generally considered safe. However, there have been documented cases of allergic reactions to PVP/povidone, particularly regarding subcutaneous (applied under the skin) use and situations where the PVP has come in contact with autologous serum (internal blood fluids) and mucous membranes. For example, a boy having an anaphylactic response after application of PVP-I (PVP-Iodine) for treatment of impetigo was found to be allergic to the PVP component of the solution. A woman, who had previously experienced urticaria (hives) from various hair products, later found to contain PVP, had an anaphylactic response after povidone-iodine solution was applied internally. She was found to be allergic to PVP. In another case, a man experiencing anaphylaxis after taking acetaminophen tablets orally was found to be allergic to PVP.

Povidone is commonly used in conjunction with other chemicals. Some of these, such as iodine, are blamed for allergic responses, although testing results in some patients show no signs of allergy to the suspect chemical. Allergies attributed to these other chemicals may possibly be caused by the PVP instead.

B) Croscarmellose sodium

Synonyms : Ac-Di-Sol; Cross linked carboxymethylcellulose sodium; explocel; modified cellulose gum; primellose; solutab.

Chemical name : Cellulose, carboxymethyl ether, sodium salt, cross linked.

Nonproprietary name : BP: Croscarmellose sodium.

PhEur: Carmellosumnatricumconexum.

USPNF: Croscarmellose sodium.

Functional category : Tablet and capsule disintegrant.

Molecular weight : 90000 - 700000

Melting point : It brown at approximately 227^0C chars at approximatrly252^oC

Description : Croscarmellose sodium occurs as an odorless, white or grayish White Powder.

Solubility : Insoluble in water, but rapidly swells 4 to 8 times it's original Volume on contact with water.

Application : Croscarmellose sodium is used in oral pharmaceutical formulation as a disintegrant for capsules, tablets, and granules.

In tablet formulations, Croscarmellose sodium may be used in both direct compression and wet granulation processes. When used in wet granulations, the Croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant,

although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet granulation process.

Stability and storage conditions:

Croscarmellose sodium is a stable though hygroscopic material. A modal tablet formulation prepared by direct compression, with Croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30 ^{0}C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

C) Cellactose 80 :

Synonyms: Elcema P-100, Ludipress.

Nonproprietary names: BP: Cellactose 80.

PhEur: Alfa-lactose monohydrate

USPNF: Cellactose 80.

Functional category: Tablet and capsule disintegrant.

Description:

Cellactose 80 is a spray dried mixture of 75 parts lactose monohydrate and 25 parts cellulose powder.Cellactose 80 is a white or almost white, odourless and tasteless powder, partly soluble in water. Apart from good flowability, it has good compactibility. The compactibility is attributed to a synergistic effet of consolidation by fragmentation of lactose and plastic deformation of cellulose. Because the lactose covers the cellulose fibers, moisture sorption is much lower than that of microcrystalline cellulose alone.

Angle of repose: 32 – 35^0

Density poured: 380 (g/l)

Density tapped: 500 (g/l)

Hauser ratio:1.24

Certificate of Analysis

(Molkerei MEGGLE Wasserburg Gmbh & Co. KG)

Table no.6.2

	Method/Specification	**Result**
Identification		
A.Cellactose 80	IR-absorption	Conforms
B. Lactose	Ph.Eur./Monogr. Cellactose 80	
C. Cellulose powdered	Thin layer chromatography	Conforms
	Ph.Eur./Monogr. Cellactose 80	
	1.Method A	Conforms
	Ph.Eur./Monogr. Cellactose 80	
	2.Method B	Conforms
Tests	USP/NF/Monogr. Cellactose 80	
pH	Ph.Eur./Monogr./4.0-7.0	
Loss on drying	Ph.Eur./Monogr./NMT 3.5 %	5.4
Water	Ph.Eur./Monogr./4.0-7.0 %	
Sulphated ash	Ph.Eur./Monogr./NMT 0.2 %	1.1
Heavy metals	Ph.Eur./Monogr./NMT 5 ppm	
Partical size distribution		4.41

		0.21
	<32 µm NMT 20 % <160 µm 35 – 65 % <250 µm NLT 80 %	conforms
Microbial contamination		
Total viable aerobic count		
Mould		
Yeasts	Ph. Eur./NMT 10^2/g	conforms
Escherichia coli	Ph. Eur./NMT 10/g	
Salmonella spp.	Ph. Eur./NMT 10/g	conforms
Assay	Ph. Eur./negative /10g	
Lactose as monohydrate	Ph. Eur./negative /10g	conforms
calculated on dried basis		
Cellulose powdered calculated on dried basis	Monogr./ 73,0-77,0 %	
	Monogr./ 23,0-27,0 %	3

Feature:

- Good content uniformity through low segregation tendency of the active ingredient
- Ideal surface structure of the cores for easy and economical coating
- Compaction of delicate active ingredients through excellent compressibility
- Consistent tablet hardness through constant lactose / cellulose ration
- High weight consistency at all compaction speeds through good flowability

- High degree of whiteness of tablets

Organic volatile impurities:

It is stated that no organic solvents are used in the manufacturing process of Cellactose 80.

Storage:

At room temperature, in tightly closed containers, under dry and odour free conditions.

Pharmaceutical Applications:

- Herbal extract tablets
- Chewable tablets
- Mineral salt tablets
- Cores for coating
- Oblong tablets

Regulatory status:

Included in the FDA inactive ingredients guide (oral capsule and tablets) included in nonparental medication licensed in the UK

D) Microcrystalline cellulose (MCC) :

Synonyms : Avicel, cellulose gel, emocel, fibrocel, tabulose, vivacel

.**Chemical name** : Cellulose

Chemical formula : $(C_6H_{10}O_5)$

Molecular weight : 36,000

Non proprietary name : BP Microcrystalline cellulose

PhEur: Cellulosum microcrystalline cellulose

USPNF: microcrystalline cellulose

Melting point : Chars at 260-270^{O}C

Nominal mean partical size: 100µm

Specific surface area : 1.21-1.30m^2/g

Description :

Microcrystalline cellulose is purified partially depolymerized cellulose that occurs as a white colored, odourless crystalline powder composed of porous particles. It is commercially available at different size grades, which have different properties and applications.

Property of some commercially available grade of microcrystalline cellulose:

Table. No. 6.3

Grade	**Nominal mean partical size (µm)**	**Moisture content (%)**
Avicel PH 101	50	≤ 5.0
Avicel PH 102	100	≤ 5.0
Avicel PH 103	50	≤ 3.0
Avicel PH 105	20	≤ 5.0
Avicel PH 112	100	≤ 1.5
Avicel PH 113	50	≤ 1.5
Avicel PH 200	180	≤ 5.0
Avicel PH 301	50	≤ 5.0
Avicel PH 302	100	≤ 5.0

Pharmaceutical application of Avicel:

Table. No. 6.4

USE	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule diluents	20-90
Tablets disintegrant	5-15
Tablet binder/ Diluents	20-90

Application:

Microcrystalline cellulose is widely used in pharmaceuticals primarily as diluents in oral tablet and capsule formulations, where it is used in both wet granulation and direct compression processes..in addition to use as diluents, MCC also has some lubricant and disintegrant properties that make it useful in tableting. It is used as tablet disintegrant in 5-20% concentration, while as diluents 20-29% concentration is employed.

E) Aspartame :

Non-proprietary Name: USPNF

Synonyms: 3-Amino-N- (α-carboxyphenethly) succinamic acid N-methyl ester: 3 -Amino-N-(α-methoxycarbonylphenethyl) succinamic acid; APM aspartyl -L-phenylamine methyl ester: canderel: E951: Equal; methyl N -α- L -aspartyl-L-phenylalaninate; NutraSweet; Sanecta; SC -18862; Tri-Sweet.

Chemical Name: N-α-L-aspartyl-L-phenylalanine 1-methyl ester.

Empirical Formula: $C_{14}H_{18}N_2O_5$

Molecular Formula : 294.31

Melting Point: 246-247^{O}C

Density (bulk): 0.4-0.5 g/cm^3 for granular grade.

0.3-0.4 g/cm^3 for powder grade.

pH: ≤4.0-6.5 (0.8%w/v aqueous solution).

Functional Category: sweetening Agent.

Description: Aspartame occurs as an off-white almost odourless, crystalline powder with an intensely sweet taste.

Application in Pharmaceutical Formulation or Technology:

Aspartame is used as an intense sweetening agent in beverage product, food product, and table-top sweetener and in pharmaceutical preparations including tablets powder mixture and vitamin preparation. It enhances flavour system and can be used to mask some unpleasant taste characteristics the approximate sweetening power is 180-200 times of sucrose.

Unlike some other intense sweetener, aspartame is metabolized in the body and consequently has some nutritive value 1g provide approximate 17 kJ (4 kcal). However in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

Stability and Storage condition:

Aspartame is stable in condition. In the presence of moisture, hydrolysis occur to form the degradation product L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2, 5-diketonepiperazine. A third degradation product is also know, β-L-aspartyl-L-phenylalanine methyl ester. For stability profile at 25^{o}C in aqueous buffers.

Stability in aqueous solution has been enhanced by the addition of cyclodextrins and by the addition of polyethylene glycol 400 at pH 2. However at pH 3.5-4.5 stability is not enhanced by the replacement of with water solvent.

F) Magnesium stearate:

Non-proprietary name: BP: Magnesium stearate

PhEur: Magnesiistearas

USPNF: Magnesium stearate

Synonyms: E 572, Hyqual, Magnesium salt.

Chemical name: Octadecanoic acid Magnesium Salt.

Empirical Formula: $C_{36}H_{70}MgO_4$

Molecular Formula: 591.27

Functional category: Tablet and capsule lubricant

Flowability: Poorly flowing, cohesive powder

Melting point: 88.5^{o}C

Moisture content: 3.85%

Solubility: Practically insoluble in ethanol, ethanol 95%, ether and water ; slightly soluble in warm benzene and warm ethanol 95%.

Description: Magnesium stearate is a fine, white, precipitated or milled, implantable powder of low bulk density having a faint, characteristic odour and taste, the powder is greasy to touch and readily adheres to the skin.

Polymerisation:

A trihydrate, acicular from and a dehydrate lamellar form have been isolated with the latter processing the better lubricating properties.

Stability and storage condition:

Magnesium stearate is stable and should be stored in a well-closed container in a cool and dry place.

Incompatibilities:

Incompatible with strong acid, alkalis and iron salts. Avoid mixing with strong oxidizing material.

Safety:

Magnesium stearate is used as a pharmaceutical excipients and is generally regarded as being nontoxic following oral administration. However oral consumption of large quantities may result in some laxative effect or mucosal irritation. Inhalation of magnesium stearate powder is harmful and has resulted in fatalities.

Handling precaution:

Observe normal precaution appropriate to the circumstances and quantity of material handled. Eye protection and glove are recommended

G) Mannitol

Chemical name: hexanitro mannitol

Synonym: mannitol hexanitrate, nitromannite, nitromannitol, nitranitol, mannitrin

IUPAC: (2R,3R,4R,5R)-Hexane-1,2,3,4,5,6-hexol-1,2,3,4,5,6-hexanitrate

Molecular formula: $C_6H_8N_6O_{18}$

Molar mass: 452.15712

Density: 1.604 g/cc

Melting point: 112 °C = 234 °F

Formula: $C_6H_{14}O_6$

Mol. mass: 182.172

Bioavailability:

In pharmacology, **bioavailability** is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered

intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient (due to inter-individual variation). Bioavailability is one of the essential tools in Pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

For dietary supplements, herbs and other nutrients in which the route of administration is nearly always oral, bioavailability generally designates simply the quantity or fraction of the ingested dose that is absorbed. Bioavailability is defined slightly differently for drugs as opposed to dietary supplements primarily due to the method of administration and Food and Drug Administration regulations.

Use: This polyol is used as an osmotic diuretic agent and a weak renal vasodilator Mannitol is also the first drug of choice for the treatment of acute glaucoma in veterinary medicine. It is administered as a 20% solution IV. It dehydrates the vitreous humor and, thus, lowers the intraocular pressure. However, it requires an intact blood-ocular barrier to work. Mannitol can also be used to temporarily encapsulate a sharp object (such as a helix on a lead for an artificial pacemaker) while it is passed through the venous system. Because the mannitol dissolves readily in blood, the sharp point will become exposed at its destination.

Mannitol may be administered in cases of severe Ciguatera poisoning. Severe ciguatoxin, or "tropical fish poisoning" can produce stroke-like symptoms. Mannitol is the primary ingredient of Mannitol Salt Agar, a bacterial growth medium, and is used in others. In oral doses larger than 20 g, mannitol acts as an osmotic laxative, and is sometimes sold as a laxative for children

Toxicology: Mannitol is contraindicated in patients with anuria and Congestive Heart Failure

H) Menthol

IUPAC name: (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol

Synonym: 3-*p*-Menthanol, Hexahydrothymol, Menthomenthol, peppermint camphor

Molecular formula: $C_{10}H_{20}O$

Molar mass: 156.27 g mol^{-1}

Appearance: White or colourless crystalline solid

Density: 0.890gcm^{-3}, solid (racemic or (−)-isomer)

Melting point: 36–38 °C (311 K), racemic 42–45 °C (318 K), (−)-form (α) 35-33-31 °C, (−)-isomer

Boiling point: 212 °C (485 K)

Solubility in water: Slightly soluble, (−)-isomer

Thermodynamic data: Phase behaviour Solid, liquid, gas

Applications

- In non-prescription products for short-term relief of minor sore throat and minor mouth or throat irritation

  Examples: lip balms and cough medicines

- As an antipruritic to reduce itching
- As a topical analgesic to relieve minor aches and pains such as muscle cramps, sprains, headaches and similar conditions, alone or combined with chemicals like camphor, eucalyptus oil or capsaicin. In Europe it tends to appear as a gel or a cream, while in the US patches and body sleeves are very frequently used

  Examples: Balm, or Icy Hot patches or knee/elbow sleeves

- In decongestants for chest and sinuses (cream, patch or nose inhaler)

Examples: Vicks Vaporub, Mentholatum, vapoRem

- In certain medications used to treat sunburns, as it provides a cooling sensation (then often associated with aloe)
- As an additive in certain cigarette brands, for flavour, to reduce the throat and sinus irritation caused by smoking.
- Commonly used in oral hygiene products and bad-breath remedies like mouthwash, toothpaste, mouth and tongue-spray, and more generally as a food flavour agent; e.g. in chewing gum, candy
- In a soda to be mixed with water to obtain a very low alcohol drink or pure (brand Ricqlès which contains 80% alcohol in France). The alcohol is also used to alleviate nausea, in particular motion sickness, by pouring a few drops on a lump of sugar.
- As a pesticide against tracheal mites of honey bees
- In perfumery, menthol is used to prepare methyl esters to emphasize floral notes (especially rose)
- In first aid products such as "mineral ice" to produce a cooling effect as a substitute for real ice in the absence of water or electricity (Pouch, Body patch/sleeve or cream)
- In various patches ranging from fever-reducing patches applied to children's foreheads to "foot patches" to relieve numerous ailments (the latter being much more frequent and elaborate in Asia, especially Japan: some varieties use "functional protrusions", or small bumps to massage ones feet as well as soothing them and cooling them down)
- In some beauty products such as hair-conditioners, based on natural ingredients (e.g. St. Ives).

7. EXPERIMENTAL

7.1 MATERIALS USED

Table No. 7.1: List of materials used and their suppliers

SR. NO.	MATERIALS	SUPPLIERS
1	Cinnarizine	Glenmark API Private LTD
2	Cellactose 80	Molkerei MEGGLE Wasserburg GmbH & Co.KG.
3	Crosspovidone	BOAI NKY Pharmaceuticals.LTD, CHINA
4	Croscarmellose sodium	MAXWELL Life science PVT.LTD,Mumbai
5	Aspartame	Changmao Biochemical Engineering co.LTD, China
6	Microcrystalline cellulose (Avicel PH-102)	Vijlak Phrma Jinnaram, Mandal
7	Lactose	SCHREIBER Dynamix Dairies.LTD Baramati
8	Mannitol	Shandong Tianli Pharmaceutical.co.LTD,China
9	Menthol	Bright Aromatics
10	Magnesium Stearate	Nitika Chemicals Ltd. Nagpur
11	Hydrochloric acid	Thermo Fisher Scientific India PVT.LTD. Mumbai
12	Sodium hydroxide pellets	Thermo Fisher Scientific India PVT.LTD. Mumbai
13	Potassium dihydrogen Orthophosphate	Qualjgens Fine Chemicals, Navi Mumbai
14	Potassium chloride	Ranbaxy Fine Chemicals Ltd., New Delhi
15	Potassium bromide (IR)	Qualigence Laboratories, Navi Mumbai.

7.2 INSTRUMENTS USED

Table No. 7.2: List of instruments used and their manufacturer

SR. NO.	INSTRUMENTS	MANUFACTURER
1	Rotary Press Tablet Compression Machine	RIMEK Minipress-I, Karnavati Engineering Ltd., Mehsana, Gujarat.
2	Dhona Balance	Dhona Instruments Pvt. Ltd., Kolkata.
3	Digital pH meter	Model No. NIG 333, Naina Solaris Ltd. India.
4	Monsanto Hardness tester	Cadmach Machinery Pvt. Ltd., Ahmedabad.
5	Roche Friabilator USP XVIII	Model No. EF-1W, Electrolab Pvt. Ltd., Goregaon (E), Mumbai.
6	Sieves	Sethi Standard Test Sieves
7	Double Beam UV-Spectrophotometer	Techcomp UV 2300
8	Dissolution Apparatus USP XVIII	Model No. TDT – 06P, Electrolab Pvt. Ltd., Goregaon (E), Mumbai.
9	FTIR Spectrophotometer	Model No. 8400 S, Shimadzu Asia Pacific Pvt. Ltd., Singapore.
10	Digital Vernier Caliper	ASAHI, India.
11	Ultrasonicator	PCI, Mumbai.
12	Magnetic stirrer	Model No. 1MLH, Remi, Mumbai

7.3 PREFORMULATION STUDIES

Identification test for Cinnarizine;

Melting point: The melting point of Cinnarizine was determined by capillary method and checked, whether it complies with the reported ones or not.

Infrared absorption Spectrophotometry:

Cinnarizine was dried in hot air oven at 50^0C for 2 hours. The samples were prepared by mixed it thoroughly in mortar and pestle. This physical mixture was compressed under pressure of 10 Ton/nm^2 and converted in a circular disc. This disc was then placed in the scanning slot of Fourier Transform Infra-red (FT-IR) Spectrophotometer and scanned at range from 400 to 4000 cm^{-1} to obtain the FTIR of cinnarizine. Compared the spectrum with reference spectrum given in BP 2007.

Preparation of stock solution of Cinnarizine:

Weigh accurately 100.0 mg of Cinnarizine and dissolve it in 100.0ml of dilution media (respective 1M NAOH). The strength of solution was found to be 1 mg/ml. Respective dilutions were prepared using stock solution (A).

After then about 10.0 ml of stock solution was accurately pipette into a 100.0 ml of volumetric flask and make up the volume with the dilution media to get stock solution of strength 100 µg/ml. The respective dilutions were prepared using stock solution (B).

Preparation of standard calibration curve:

To make the dilutions of Cinnarizine ranging from 5 µg/ml to 25 µg/ml appropriate volumes of stock solution i.e. 5, 10, 15, 20 and 25 ml was pipetted and volume was made up to 100.0 ml with the dilution media (1M NAOH). The absorbance was measured of the prepared dilution in UV-Visible spectrophotometer at 254 nm (IP) wavelength and calibration curve between absorbance and concentration was plotted.

To obtain 5,10,15,20,25,30 µg/ml of the sample and the absorbance was measured at 254 nm by UV visible spectrophotometer. Same procedure was repeated for Acidic buffer P^H 1.2 and basic medium (1M NAOH) to prepare standard curve. Reagents required for preparation of pH 1.2 hydrochloric acid buffer and basic medium are given as follows:

Preparation of Reagents:

The reagents were prepared as per IP.

a) **Preparation of 1M Sodium hydroxide (NAOH) solution:** NAOH pallets dissolve with distilled water so that final solution contains 42 g of sodium hydroxide in 1000.0 ml to obtain 1M sodium hydroxide solution.

b) **Preparation of 0.2M hydrochloric acid (HCl) solution:** Conc. HCl diluted with distilled water so that final solution contains 7.292 g of hydrochloric acid in 1000.0 ml to obtain 0.2M hydrochloric acid solution.

a) **Preparation of 0.2M potassium chloride (KCl) solution:** Dissolve approx. 14.911 g of potassium chloride in distilled water and diluted to 1000.0 ml with distilled water to obtain 0.2M potassium chloride solution.

b) **Preparation of dilution media (pH 1.2 hydrochloric acid buffer):** About 250.0 ml of 0.2M potassium chloride solution was placed in a 1000.0 ml volumetric flask. To this, about 425.0 ml of 0.2M hydrochloric acid was added and then volume was adjusted to 1000 ml with distilled water. Then prepared solution was tested using pH meter. The pH of solution was adjusted to pH 1.2 with the help of 0.2M hydrochloric acid.

8. ASSESSMENT OF PREPARED FORMULATION [7]

8.1) Pre-compression assessment of physical parameters of mixture blend

Different physical properties of mixture blend were evaluated using following methods.

Angle of Repose:

It is the maximum angle that can be obtained between the freestanding surface of a powder heap and horizontal plane. Such the measurement gives at least a qualitative assessment of internal cohesive and frictional effects under low level of external loading, as might apply in powder mixing or in tablet die or capsule shell filling operation.

Angle of repose method, which results in so-called dynamic angle, is preferred, since they most closely mimic the manufacturing situation, in which powder is in motion, with care, dynamic angle of repose measurement can be replicated with the relative standard deviations of approximately 2% they are particularly sensitive to changes in particle size distribution and to moisture content and they provide rapid means of monitoring significant batch difference in these respects.

Angle of repose is calculated by fixed funnel method. In this method funnel was fixed to a stand in such a way that the lower tip of funnel was 2 cm above the surface. A paper was placed on flat surface. The blend was allowed to fall freely on the paper through the funnel, till the tip of heap formed just touches the funnel. The height and radius of heap was noted and from this angle of repose was determined with the help of given formula.

The formula for calculating angle of repose is:

$$\tan \theta = h/r \qquad \theta = \tan^{-1}(h/r)$$

Where,

θ = angle of repose

h = height of the powder cone

r = radius of the circumference

Table No: 8.1 Angle of repose as an indication of powder flow properties:

Sr. no.	Angle of repose (Degrees)	Type of flow
1	< 20	Excellent
2	20-30	Good
3	30-34	Passable
4	> 40	Very poor

Bulk Density:

Bulk density is indicative of the packing of the particles and as such is greatly influenced by the size of blend. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas,

$$\mathbf{LBD = W/V_0}$$

$$\mathbf{TBD = W/V_t}$$

Where, W = weight of the powder

V_0 = volume of packing

V_t = tapped volume of the packing

Tapped Density:

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula,

$$\mathbf{Pt = M/Vt}$$

Where, Pt = Tapped Density

M = Weight of the sample in gm

Vt = tapped volume of blend in cm^3

Compressibility Index:

Compressibility index is a measure of flow rate of powder and measure of relative importance of inter particulate interactions. The compressibility index of the granules was determined by the Carr's compressibility index.

Carr's compressibility index (%) = [(TBD – LBD) × 100]/ TBD

Table No. : 8.2 Relationship between % Compressibility and flowability:

%compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula,

Hausner ratio = Pt/Pb

Where, Pt = tapped density,

Pb = bulk density

Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

8.2) Post-compression assessment of Oro-dispersible tablet[7]:-

Tablets were evaluated as per pharmacopoeial specifications.

Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in officials and none deviate by more than twice the percentage shown as,

Table No.8.3 : Weight variation tolerances for uncoated tablets

Average weight of tablet (in mg)		% Deviation
As per USP-30/NF-25	As per IP-2007	
130 or less	80 or less	10
From 130 through 324	80 mg < x < 250 mg	7.5
more than 324	250 mg or more	5

Hardness:

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India). Tablet was kept diagonally between the two plungers and a pressure was applied to it until the tablet broke down into two parts completely and the reading on the scale was noted down in kg/cm^2.

Friability:

Roche friabilator (ElectrolabFriabilator – USP, Model No. EF-1W) was used to test the percent friability of the tablets. The tablets should be carefully dedusted prior to testing. Tablets were placed in drum, which was then rotated for 100 revolutions. After that tablets were

removed and reweighed. The weight lost should not exceed the limit 1.0%. The percentage friability was measured using the formula,

$$\% F = [1 - (W/ W_0)] \times 100$$

Where, % F = friability in percentage

W_0 = Initial weight of tablet

W = Weight of tablets after revolution**.**

Thickness:

The thickness of the tablets was determined using a digital calliper (ASAHI, India). Five tablets from the each batch were used and average values and SDs were calculated.

Wetting time:

A piece of tissue paper folded double was placed in a Petri dish containing 6 ml of water .the tablet was placed on the paper, and time for the complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0c.Wetting time corresponding to the time taken for the tablet to disintegrate when kept motionless on the Petri dish.

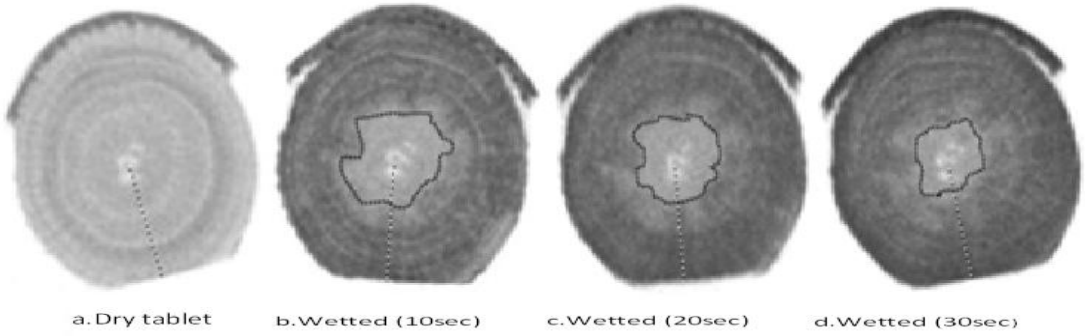


Fig no. 8.1 observation of wetting time

Tensile strength:

The tensile strength (T) of the tablets was calculated using the formula,

$$T \leq 2f/\prod dt$$

Where,

F≤ Crushing strength of the tablets

D≤ Diameter of the tablets

T≤ Thickness of the tablets

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish (7.5cm) containing 7 ml water. Tablet was put on the tissue paper & allow to wet completely. The wetted tablet was then weighed.

The water absorption ratio, R, was determined using following equation.

R = 100× (Wa-Wb)/Wb Where,

Wa = weight of a tablet after absorption

Wb = weight of a tablet before absorption

Three trials for each were performed,

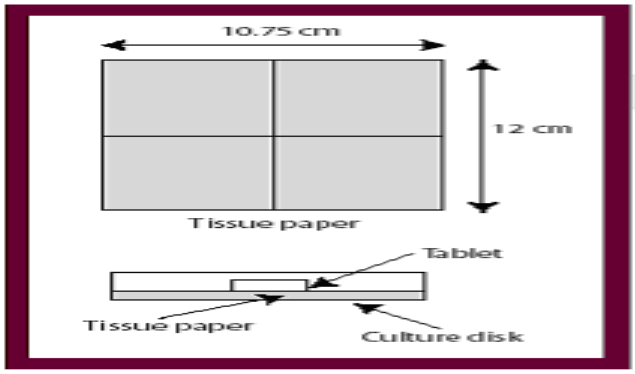


Figure Method for measuring wetting time and absorption ratio.

Fig No 8.2: method for measuring the wetting time and water absorption ratio.

Estimation of drug content [10]

The drug content uniformity was calculated on all the formulations of dispersible tablets. The study was carried out in triplicate. Table No.10.16 shows the results of the drug content uniformity in each formulation with S.D. values.

These values are found satisfactory, which ensures dosage uniformity and meets with requirements of USP (± 10% deviation).

Disintegration Time:

In vitro disintegration time of tablets from each formulation was determined by using the Digital Tablet Disintegration Apparatus. *In vitro* disintegration test was carried out at 37±2^{o}C in 900 ml distilled water.

***In-vitro* Dissolution studies[8]:**

In-vitro dissolution studies for all the fabricated tablets of Cinnarizine were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was 0.1N HCL (900ml) maintained at 37 ± 0.5^{o}C.

Aliquots of dissolution media were withdrawn (10ml) at different intervals and content of Cinnarizine was measured by determining absorbance at 292 nm. 10ml aliquot was withdrawn at the 0min, 30sec,1min,1.30min.....to be continued at the 30sec intervals and filter by whatmann filter paper. And analyzed at 292nm using-visible spectrophotometer (ELICO SL 164 Double beam UV visible spectrophotometer).

An equal volume of fresh medium, which was pre-warmed at 37^{0}c replaced in to the dissolution medium after each sampling to maintain the constant volume throughout the test. The dissolution experiment were conducted in triplicate. And the same procedure is followed using dissolution medium pH 6.8 buffer.

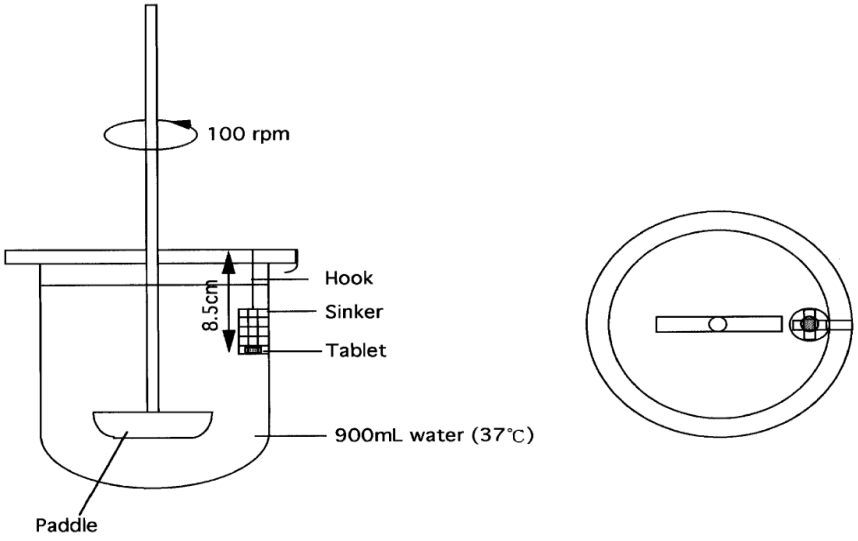


Fig no. 8.3 dissolution apparatus

Stability studies of the tablet [9]:

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a pre-determined level of labelled potency and its physical characteristic have not changed the appreciably or deleteriously. Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environment factor such as temperature, humidity and light enabling recommended storage condition, re-test periods and shelf lives.

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principle of accelerated stability studies is adopted.

The international conference on harmonization (ICH) guideline titled "stability testing of the new drug substance and product" (QIA) describes the stability test requirements for drug registrations application in the European Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

- Long term testing: $25^0c \pm 2^0c$/60% RH ± 5% for 12 months.
- Accelerated testing: $40^0c \pm 2^0c$/ 75 % RH ± 5% for 6 months.

Method:

The selected formulation were packed in tightly closed container were plugged with the cotton and capped they were then stored at 40^0c ± 2^0c/ 75 % RH ± 5% for 3 months in humidity chamber (Thermolab Mumbai) and valuate for their physical appearance and drug solution were further scanned to observe any possible spectral changes T80% was calculated by using dissolution studies.

9.1 Formulation Design:

i) Selection of superdisintegrant

A disintegrant is included in the formulation to ensure that the tablet, when in the contact with a liquid, breaks up into small fragments, which promotes rapid drug dissolution. Ideally, the tablet should break up into individual drug particles in order to obtain the largest possible effective surface area during dissolution.

The disintegration process for tablet occurs into two steps. First, the liquid wets the solid and penetrates the pores of the tablet. Thereafter, the tablet breaks into smaller fragments. A disaggregation directly into primary powder particles will set up the conditions for the possible dissolution of the drug.

The disintegration times of these tablets depend largely on the size of dosage form and hardness parameter. The basic approach used in the development of the Oral dispersible tablet is the use of superdisintegrants.

Preliminary study was carried out for screening of three superdisintegrants namely,

1) Crospovidone
2) Croscarmellose
3) Cellactose80

Drug, mannitol, aspartame, magnesium stearate, microcrystalline cellulose and various concentrations of superdisintegrants were taken and compressed by direct compression method. The weight of tablet in all batches were kept the constant. All the batches of tablets were prepared by Direct compression method using 21- station rotary tablet machine (Rimek machineries Ltd).Effect of disintegrating agents and their concentrations on various tablets properties and in-vitro dissolution characteristics were studied and discussed.

Table 9.1 Formulation design of tablets (All conc. are in mg)

Sr.no	Ingredients	Af1	Af2	Af3	Bf1	Bf2	Bf3	Cf1	Cf2	Cf3
1.	Cinnarizine	25	25	25	25	25	25	25	25	25
2.	Crospovidone	10	15	20	_	_	_	_	_	_
3.	Croscarmellose	_	_	_	10	15	20	_	_	_
4.	Cellactose80	_	_	_	_	_	_	10	15	20
5.	Lactose	20	20	20	20	20	20	20	20	20
6.	Microcrystalline cellulose	35	30	25	35	30	25	35	30	25
7.	Magnesium stearate	5	5	5	5	5	5	5	5	5
8.	Sodium lauryl sulphate	2	2	2	2	2	2	2	2	2
9.	Menthol	2	2	2	2	2	2	2	2	2
10	Aspartame	10	10	10	10	10	10	10	10	10
11.	Mannitol	91	91	91	91	91	91	91	91	91
	Total	200	200	200	200	200	200	200	200	200

ii) Preparation of powder blends of Drug and Excipients:

Oral dispersible tablets of Cinnarizine was prepared using direct compression method after incorporating different superdisintegrants such as, Croscarmellose sodium (Ac-Di-Sol) and Cellactose80 in different concentrations.

Avicel PH 101 (MCC), Mannitol as directly compressible diluents, Ac-Di-Sol, crospovidone and Cellactose80 were tried as superdisintegrants. the efficacy of these super disintegrants in any fast dissolving dosage forms depends upon its selection, concentration used, method of incorporation and steps used for preparation and / phycochemical characteristics of the formulation.

All the ingredients were passed through 60 mesh sieve separately and then ingredients were weighed and mixed in a geometrical order. First MCC, Mannitol and superdisintegrants were weighted and mixed together. Then drug and aspartame complex mixer

is added in first mixer and finally magnesium stearate was added and mixed for 10-15min. The tablets were then compressed using 12 mm size punches to get a tablet of 200 mg.

Before tablet preparation, the mixture blend of all the formulation were subjected for compatibility studies I.R. and pre-compressible parameters like angle of repose, bulk density, tapped density, compressibility index and Hauser's ratio.

The Oro-dispersible tablets prepared subjected to post compression parameters like hardness, friability, weight variation, wetting time, water absorption ratio, *in-vitro* dissolution and *in-vitro* disintegration. Tablet compression was carried out in rotary compression machine. Compression force was kept constant throughout the study. Compression was carried out using 7.5 mm concave faced punches. Multiple Punch Single Rotary, Rimek Tablet Compression Machine according to the 1, 2, 3, 4, 5,..... a total number of nine formulations were prepared and weight of all tablets kept constant.i.e 200 mg.

PREPARATION OF CINNARIZINE ORAL DISPERSIBLE TABLETS BY DIRECT COMPRESSION :

The tablets were prepared by direct compression method. Weigh of all ingradients as formula then mix well. Taken well mixed all ingredients, then that blend was punched at low pressure in 12mm punch on 21 station "B" tooling rotator tablet punching machine (RIMEK MUMBAI). The tablets are forms.

9. RESULTS AND DISCUSSION

The present work was aimed to find out the effects of various superdisintegrants on the dissolution profile and various properties of oral dispersible tablets of Cinnarizine.

9.1 PREFORMULATION STUDIES

a) Identification test for Cinnarizine.

i. Melting point: The melting point of the Cinnarizine was found to be 118^0C-120^0C, which complies with melting point reported ones.

ii. Infrared absorption spectrophotometry: All the prominent and primary peaks were observed in FTIR spectrum of Cinnarizine (*Fig. 10.1)* and match with the reference spectrum.

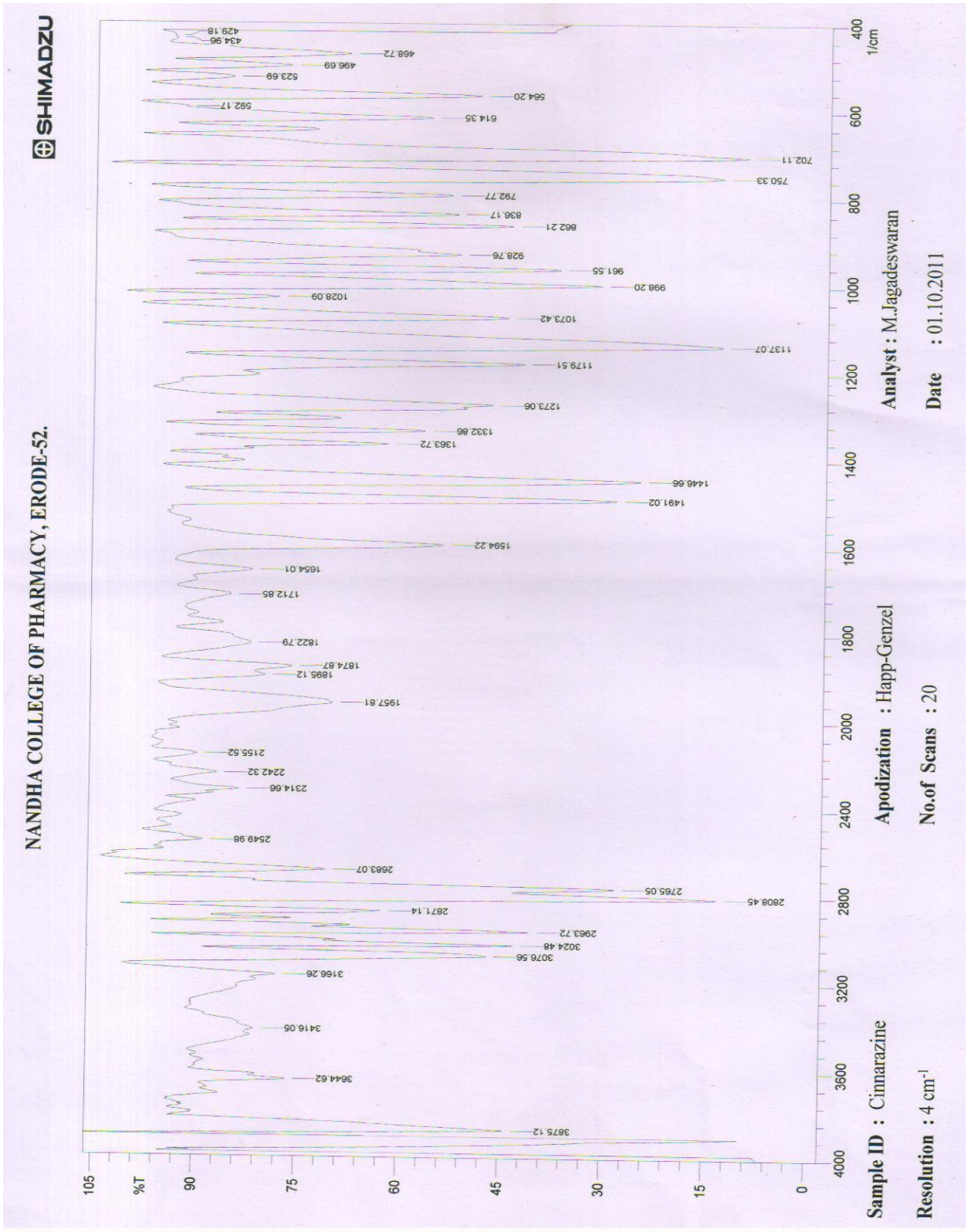


Figure 10.1: FTIR Spectrum of drug sample.

9.2.) Standard calibration curve of Cinnarizine in hydrochloric acid buffer pH 1.2:

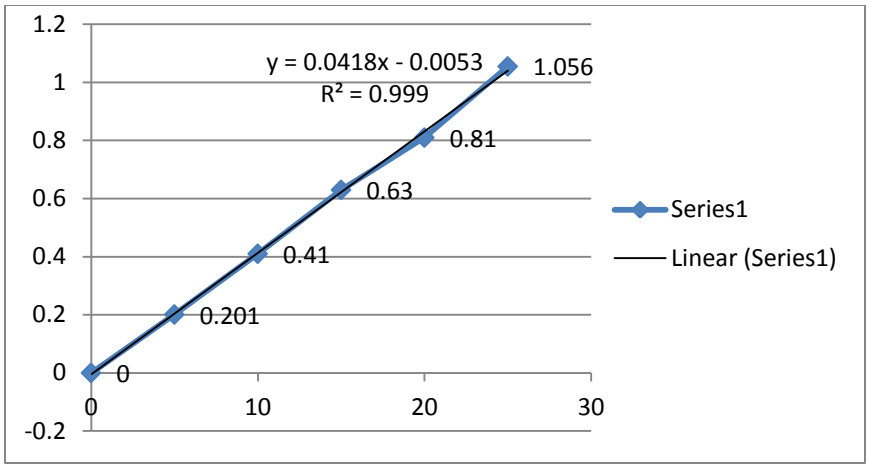
i) Qualitative identification: 30 µg/ml solution of Cinnarizine was prepared in HCl buffer pH 1.2 and was subjected to scanning under UV visible spectrophotometer, between 200-400 nm. The λ_{max} was found to be at 254 nm.

ii) Preparation of standard calibration curve in HCl buffer pH 1.2:

Standard calibration curve was prepared for concentration of 5µg/ml to 25µg/ml at 254 nm. The graph of absorbance v/s concentration was plotted and data were subjected to linear regression analysis. The standard calibration curve of drug in HCl buffer pH 1.2 was as depicted in *Figure* 9.2 The data had correlation coefficient of 0.999 and equation of regressed line is, **y=0.041X+0.005**

Table No. 10.1: Absorbance values for standard calibration curve of Cinnarizine in hydrochloric acid buffer pH 1.2

Sr. No.	Concentration (µg/ml)	Absorbance
1	**0**	**0**
2	**5**	**0.201**
3	**10**	**0.410**
4	**15**	**0.630**
5	**20**	**0.810**
6	**25**	**1.054**



Graph 10.1: Standard calibration curve of Cinnarizine in pH 1.2 buffer

The calibration curve for Cinnarizine in pH 1.2 buffers in the concentration range of 5µg/ml to 25µg/ml was a straight line. The absorbance increased with the increase in concentration. Thus the standard curve followed the Beer-Lambert's Law.

9.3) Standard calibration curve of Cinnarizine in phosphate buffer pH 6.8:

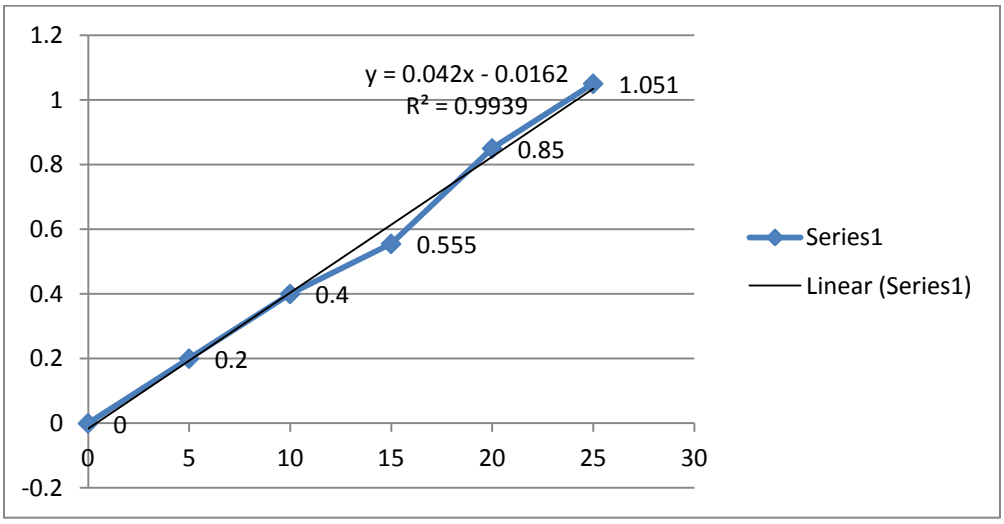
a) Qualitative identification: 30 µg/ml solution of Cinnarizine was prepared in phosphate buffer pH 6.8 and was subjected to scanning under UV visible spectrophotometer, between 200-400 nm. The λ_{max} was found to be at 254 nm. *(Figure 9.5).*

As described earlier in section *3.5.5* standard calibration curve was prepared for concentration of 5µg/ml to 25µg/ml at 254 nm. The graph of absorbance v/s concentration was plotted and data were subjected to linear regression analysis. The standard calibration curve of drug in phosphate buffer pH 6.8 was as depicted in *Figure* 9.5 The data of absorbance is as shown in *Table* 9.2 The data had correlation coefficient of 0.998 and equation of regressed line is,

y = 0.042x - 0.016

Table No. 10.2: Absorbance values for standard calibration curve of Cinnarizine in phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance
1	**0**	**0**
2	**5**	**0.20**
3	**10**	**0.400**
4	**15**	**0.555**
5	**20**	**0.850**
6	**25**	**1.051**



Graph 10.2: Standard Calibration curve of Cinnarizine in pH6.8 buffer

Colour, odour, taste and appearance:

Table . 10.3 Parameter Drug Powder

Sr.no	Parameter	Drug
1	Colour	White
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Amorphous powder

Drug and Excipients compatibility studies:

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and all Excipients. About 100 mg of this mixture was compressed to from a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to400cm-1 in a **Perkin Elmer FTIR Spectrophotometer.** The IR spectrum of the physical mixture was done to detect any appearance or disappearance of peaks.

The compatibility between the drug and excipients were evaluated using FTIR matching method. The IR spectra of physical mixture are shown in figure.

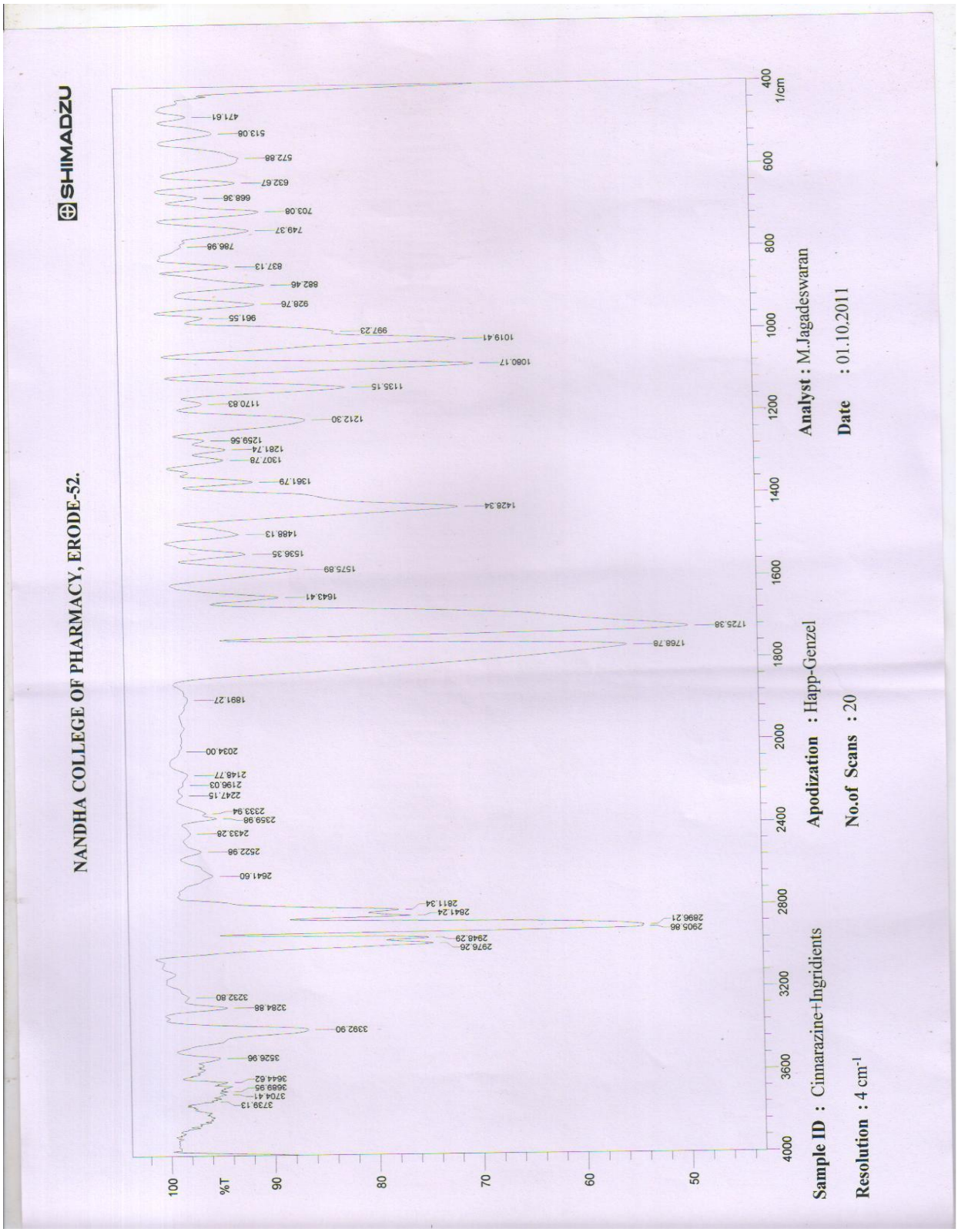


Figure no.10.2 FTIR spectrum of Physical mixture

Cinnarizine (IR Spectra):

Cinnarizine shows the C=C aromatic stretching at 1594.22 & 1491.02cm^{-1}, N-H at 3416.05$cm^{-1,}$ C-H at 3024.56cm^{-1}, CH_3 bending at 1446.66 & 1363.72cm^{1}, CH_2 bending at 1446.66cm^{-1}, Aromatic stretching at 3166.26cm^{-1}, Aromatic stretching out of plane 862.21cm^{-1}, C=C alkaane 1594.22cm^{-1}

Drug and physical mixture (IR spectra):

Cinnarizine with physical mixture shows C=C at 1575 &1488.13cm^{-1}, N-H at 3392.90cm^{-1}, C-H at 3024.56cm^{-1}, CH_3 bending at 1428.34 & 1361.79cm^{-1}, CH_2 bending at 1428.34cm^{-1}, Aromatic stretching at 2976.26cm^{-1}, Aromatic stretching out of plane at 882.46cm^{-1}, C=C alkane at 1536.35cm^{-1}, C=O at 1712.85cm^{-1}, O-H at 3416.05cm^{-1}

Pre-compression study of tablet blend:

Nine formulations were prepared by using 5%, 7.5%, 10% concentration of superdisintegration of superdisintegrants croscarmellose, crospovidone and cellactose80. For each desined formulation, powder mixed blend of drug and excipients was prepared and evaluated for various parameters as follows.

Angle of Repose (θ***):***The and angle of repose of various powder mixed blend, prepared with different superdisintegrants, was measured by the cylinder method. Angle of repose was found in the range from 27.25 to 33.27 the good flowability of powder blend was also evidenced with angle of repose which is indicated a good flowability. The result are given in table no 10.4

Table no 10.4

Batch code	Angle of repose (θ)
Af_1	30.96
Af2	31.21
Af3	30.60
Bf1	31.60
Bf2	32.46
Bf3	33.27
Cf1	30.45
Cf2	27.25
Cf3	28.51

Bulk density: The bulk density of various powder mixed blends. Prepared with the different superdisintegrants was measured by graduated cylinder. The bulk density was found in the range from 0.5 to 0.526 The result are presented in Table no 10.5

Table no.10.5.

Batch code	Bulk density (gm/cm^3)
Af_1	0.5
Af2	0.5263
Af3	0.5
Bf1	0.5
Bf2	0.520
Bf3	0.526
Cf1	0.520
Cf2	0.519
Cf3	0.524

Tapped density: The tapped density of various powder mixed blends prepared with different superdisintegrants, was measured by the measuring cylinder. The tapped density was found in the range from 0.602 to 0.627. The result are given in Table no. 10.6

Table no.10.6.

Batch code	Tapped density (gm/cm^3)
Af_1	0.602
Af2	0.625
Af3	0.625
Bf1	0.602
Bf2	0.617
Bf3	0.609
Cf1	0.621
Cf2	0.627
Cf3	0.628

Compressibility Index: The compressibility index of various powder mixed blends prepared with the different superdisintegrants using bulk density and tapped density data, compressibility index was calculated. It was found in the range 15.02 to 17.22 The results are given in table no.10.7

Table no.10.7

Batch code	Compressibility Index(%)
Af_1	16.94
Af2	15.79
Af3	15.79
Bf1	16.94
Bf2	15.72
Bf3	15.02
Cf1	16.26
Cf2	17.22
Cf3	16.59

Hausner ratio: The Hausner ratio of various powder mixed blends prepared with different superdisintegrants, it was calculated by the using bulk density and tapped density data. It was found in the range of 1.17 to 1.25. The results are given in Table no.10.8

Table no.10.8

Batch code	Hausner ratio
Af_1	1.204
Af2	1.188
Af3	1.25
Bf1	1.204
Bf2	1.186
Bf3	1.17
Cf1	1.19
Cf2	1.20
Cf3	1.199

Evaluation of oral dispersible tablet of Cinnarizine:

In this work for the ease of analysis and to study the impact of various superdisintegrants on enhancing the dissolution of Cinnarizine. The experiment was design with seven formulations which were categorize into three group based on the concentration of superdisintegrants.

Weight variation: Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniforms weight due to uniform die fill. The tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications less than 7.5%. The results are given in table no 10.9

Table no.10.9

Batch code	Weight (mg) ± S.D
Af_1	199.985 ±
Af2	200.825±
Af3	199.765±
Bf1	201.01±
Bf2	200.03±
Bf3	200.81±
Cf1	201.3±
Cf2	202.61±
Cf3	199.12±

Thickness uniformity: Tablets were evaluated by using the verniercaliper. The thickness of tablets was found to be exact .3.5 uniform thickness was obtained due to uniform die fill. The result are given in table no 10.10

Tablet no.10.10

Batch code	Thickness (mm)
Af_1	3.571
Af2	3.552
Af3	3.558
Bf1	3.573
Bf2	3.568
Bf3	3.568
Cf1	3.571
Cf2	3.574
Cf3	3.60

Hardness: Tablets were evaluated by using hardness tester. Hardness of the tablets was found in the range 1.91 to 2.02. The result are given in table no 10.11

Table no.10.11.

Batch code	Hardness (kg/cm2)
Af_1	1.98
Af2	1.98
Af3	2.02
Bf1	1.95
Bf2	1.96
Bf3	2.0
Cf1	1.91
Cf2	2.02
Cf3	1.967

Friability: Tablets were evaluated by using the Roche Friabilator and Friability of tablets was observed in acceptable range 0.48 to 0.81 (Less than 1%).The results are given in table no 10.12

Table no 10.12.

Batch code	Friability (%)
Af_1	0.650
Af2	0.771
Af3	0.589
Bf1	0.7181
Bf2	0.81
Bf3	0.70
Cf1	0.48
Cf2	0.53
Cf3	0.79

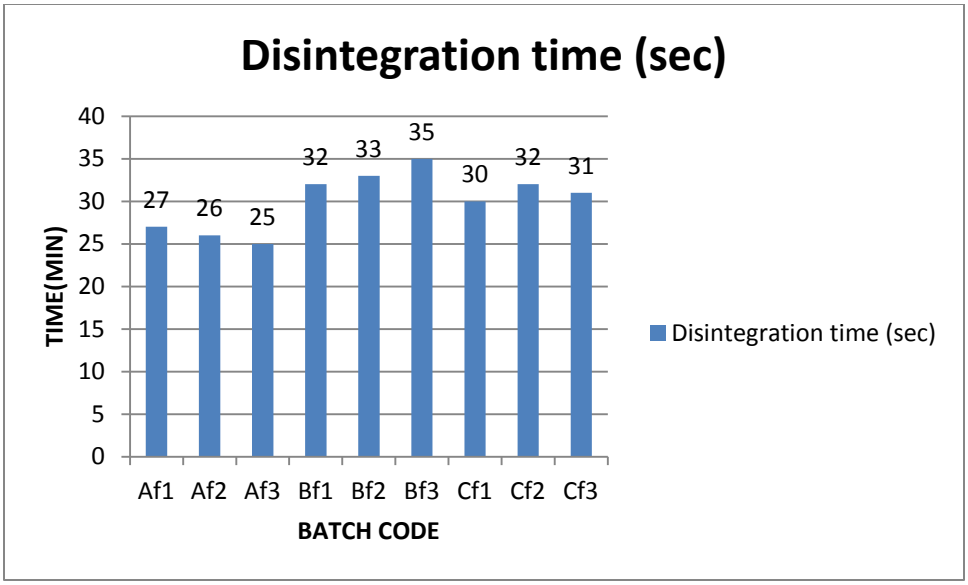
Tensile strength: The tensile strength of tablet was calculated by using the crushing strength, diameter and thickness of the tablets. It was found in the range 4.09 to 5.91 The result are given in table no.10.13 **Table no.10.13.**

Batch code	Tensile strength (kg/cm^2)
Af_1	**4.36**
Af2	**4.33**
Af3	**4.09**
Bf1	**5.73**
Bf2	**5.91**
Bf3	**5.37**
Cf1	**5.37**
Cf2	**4.99**
Cf3	**4.55**

Disintegration time: Tablets were evaluated for disintegration time in the disintegration test apparatus (I.P) The disintegration time was found in the range ..25 to 35 for all the batches. The batch **AF3** showed the fastest disintegration. The result are given in Table no.10.14

Table no.10.14.

Batch code	Disintegration time (sec)
Af_1	**27**
Af2	**26**
Af3	**25**
Bf1	**32**
Bf2	**33**
Bf3	**35**
Cf1	**30**
Cf2	**32**
Cf3	**31**



Graph No. 10.3 **Disintegration time.**

Water absorption ratio: A piece of tissue paper folded twice was placed in a small petri-dish (6.5cm) containing 6ml of water, a tablet was placed on paper and the time for complete wetting was measured the wetted tablet was then weighed and the water absorption ratio was calculated for each batch. The ratio was calculated for each batch. The ratios are given in the table no.10.15

Table no.10.15.

Batch code	Water absorption ratio ±S.D
Af_1	**82.80±5.76**
Af2	**83.09±2.45**
Af3	**60.62± 7.90**
Bf1	**90.03±6.04**
Bf2	**67.76± 3.64**
Bf3	**97.08±1.96**
Cf1	**63.18± 4.86**
Cf2	**67.76± 3.64**
Cf3	**60.62± 7.91**

Estimation of drug content :

The drug content uniformity was calculated on all the formulations of dispersible tablets. The study was carried out in triplicate. Table No.10.16 shows the results of the drug content uniformity in each formulation with S.D. values.

These values are found satisfactory, which ensures dosage uniformity and meets with requirements of USP (± 10% deviation).

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Table no.10.16

Sr.no	Batch code	Content uniformity (%)
1	Af1	95.76
2	Af2	96.06
3	Af3	99.96
4	Bf1	94.60
5	Bf2	94.63
6	Bf3	95.32
7	Cf1	92.96
8	Cf2	93.59
9	Cf3	94.07

In-vitro release studies:

The Comparative analysis of each formulation was based on in vitro kinetic parameters, which elucidated the release profile. The time taken for 80% drug release was taken as a response for comparative interpretation of superdisintegrants. The in-vitro drug release of tablets of Cinnarizine for all formulation are given as follows.

***In vitro* drug release studies details:**

Apparatus used : USP XXIII dissolution test apparatus

Dissolution medium : 0.1N HCL

Dissolution medium volume : 900 ml

Temperature : 37±0.5ºC

Speed of basket paddle : 50 rpm

Sampling intervals : 0.30 Sec

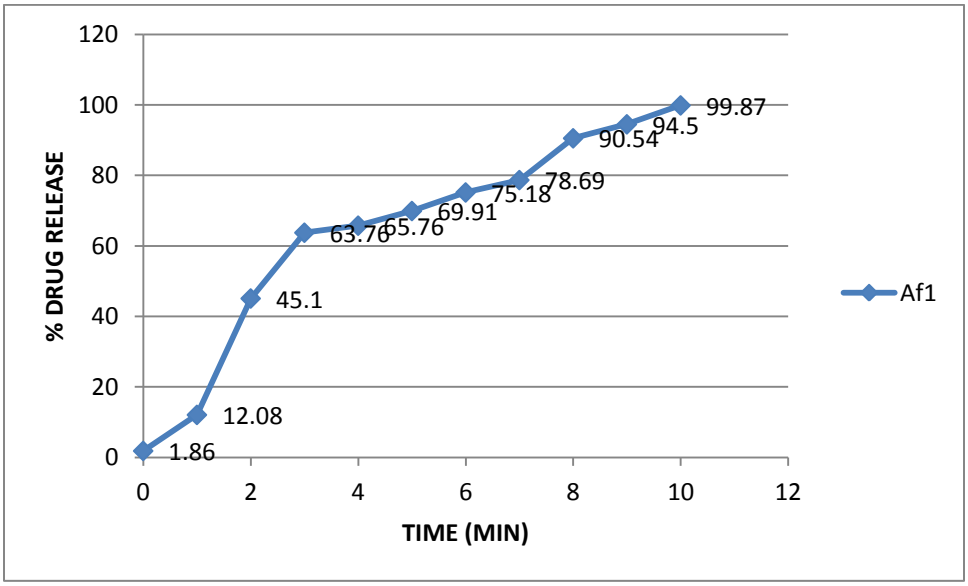
Sample withdrawn : 10 ml

Absorbance measured : 254 nm

In-vitro release studies of batch AF1in 0.1N HCL

Table no.10.17

Sr.no	Time (min)	Percent drug release
1	**0**	**1.86**
2	**1**	**12.08**
3	**2**	**45.10**
4	**3**	**63.76**
5	**4**	**65.76**
6	**5**	**69.91**
7	**6**	**75.18**
8	**7**	**78.69**
9	**8**	**90.54**
10	**9**	**94.5**
11	**10**	**99.87**

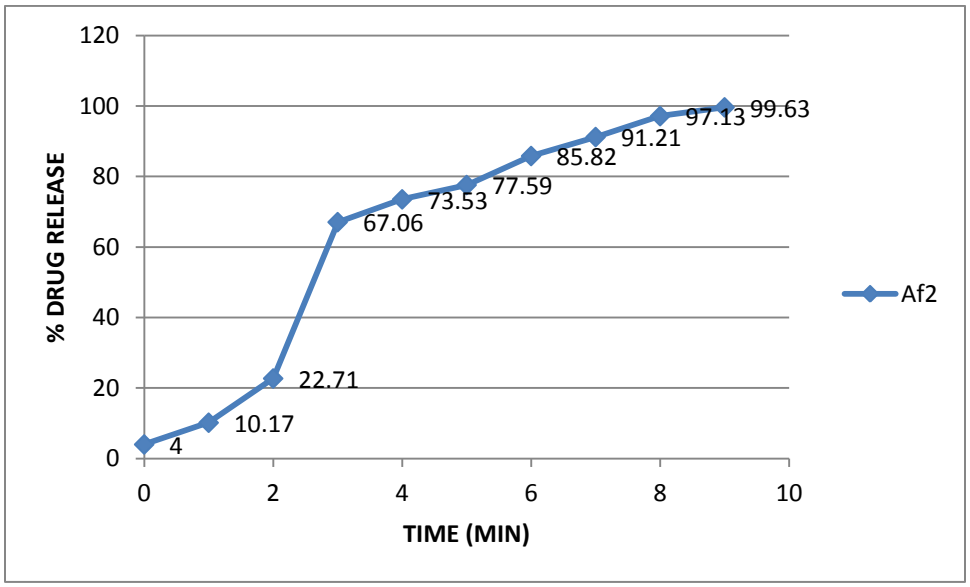


Graph. No 10.4 In-vitro release studies of batch AF1in 0.1N HCL

In-vitro release studies of batch AF2 in 0.1N HCL

Table no.10.18

Sr.no	Time (min)	Percent drug release
1	**0**	**4.0**
2	**1**	**10.17**
3	**2**	**22.71**
4	**3**	**67.06**
5	**4**	**73.53**
6	**5**	**77.59**
7	**6**	**85.82**
8	**7**	**91.21**
9	**8**	**97.13**
10	**9**	**99.63**

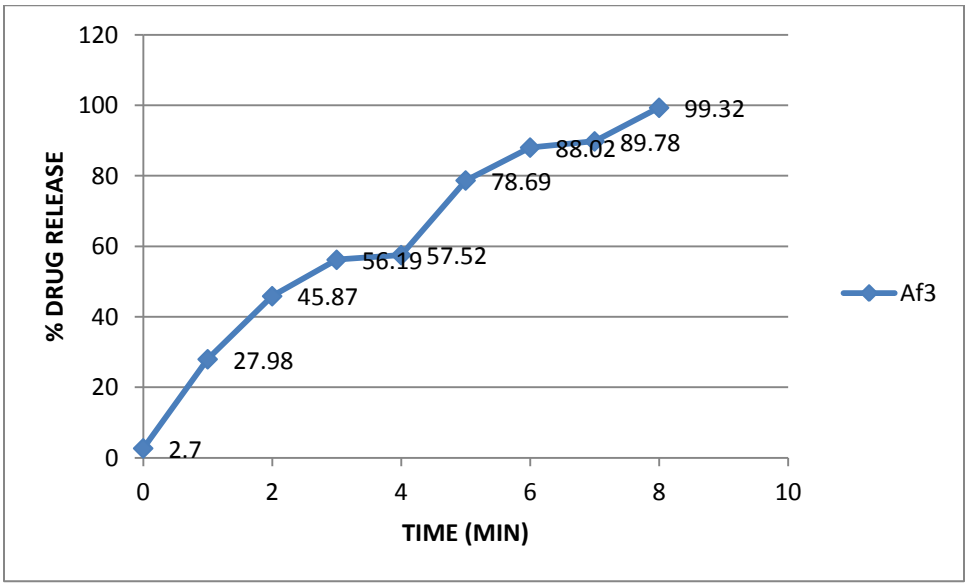


Graph. No 10.5 In-vitro release studies of batch AF2 in 0.1N HCL

In-vitro release studies of batch AF3 in 0.1N HCL

Table no.10.19

Sr.no	Time (min)	Percent drug release
1	**0**	**2.7**
2	**1**	**27.98**
3	**2**	**45.87**
4	**3**	**56.19**
5	**4**	**57.52**
6	**5**	**78.69**
7	**6**	**88.02**
8	**7**	**89.78**
9	**8**	**99.32**

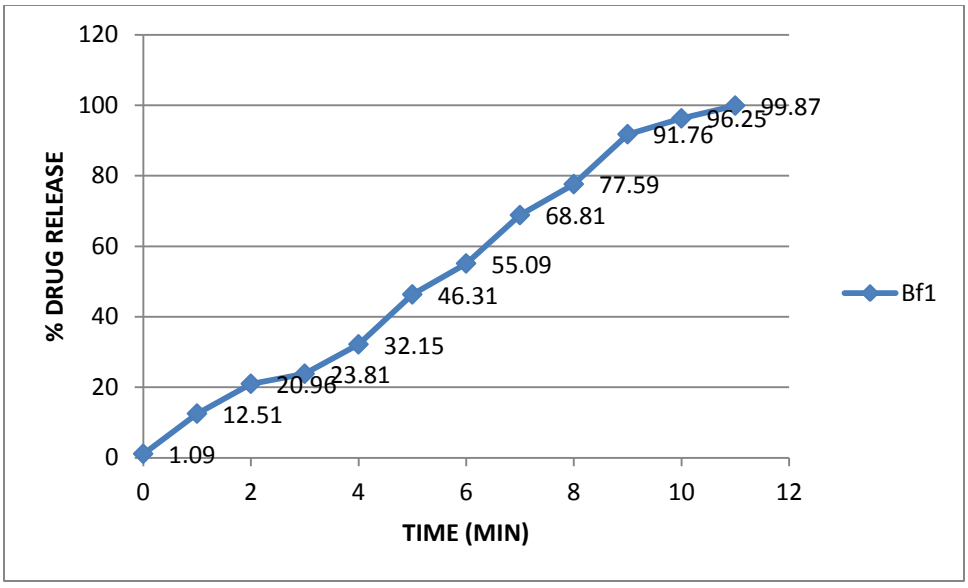


Graph No 10.6 In-vitro release studies of batch AF3 in 0.1N HCL

In-vitro release studies of batch BF1 in 0.1N HCL

Table no.10.20

Sr.no	Time (min)	Percent drug release(%)
1	**0**	**1.09**
2	**1**	**12.51**
3	**2**	**20.96**
4	**3**	**23.81**
5	**4**	**32.15**
6	**5**	**46.31**
7	**6**	**55.09**
8	**7**	**68.81**
9	**8**	**77.59**
10	**9**	**91.76**
11	**10**	**96.25**
12	**11**	**99.87**

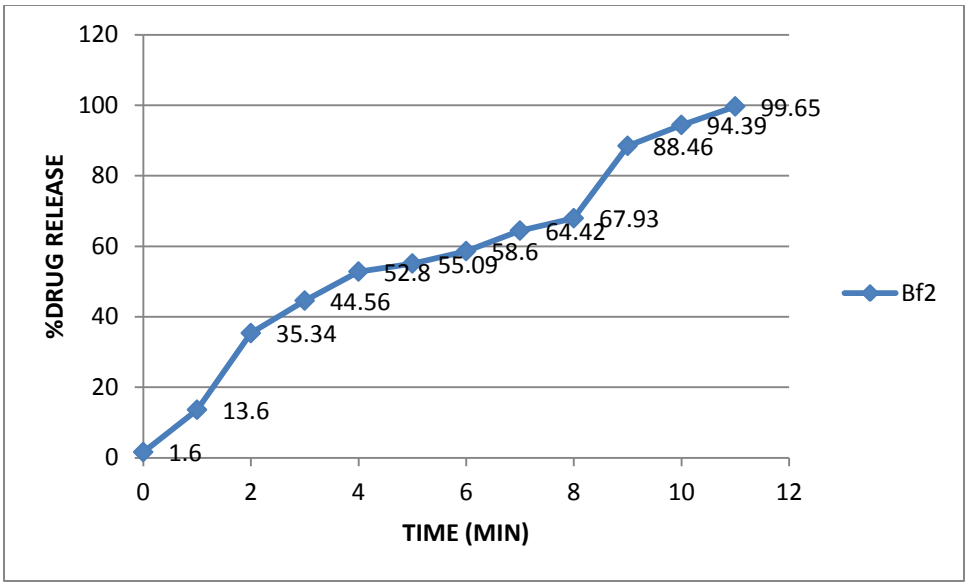


Graph No 10.7 In-vitro release studies of batch BF1 in 0.1N HCL

In-vitro release studies of batch BF2in 0.1N HCL

Table no.10.21.

Sr.no	Time (min)	Percent drug release(%)
1	**0**	**1.6**
2	**1**	**13.60**
3	**2**	**35.34**
4	**3**	**44.56**
5	**4**	**52.80**
6	**5**	**55.09**
7	**6**	**58.60**
8	**7**	**64.42**
9	**8**	**67.93**
10	**9**	**88.46**
11	**10**	**94.39**
12	**11**	**99.65**

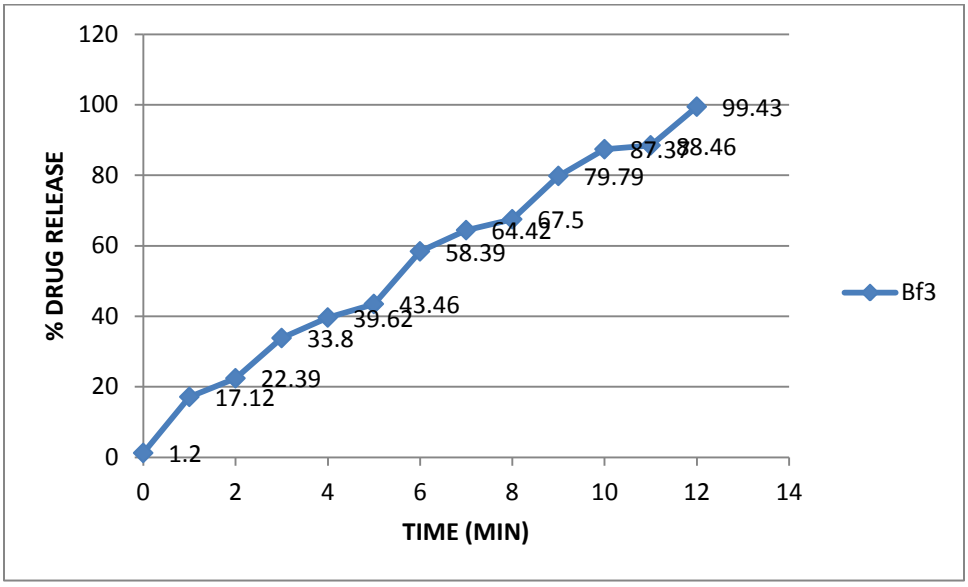


Graph No 10.8 In-vitro release studies of batch BF2in 0.1N HCL

In-vitro release studies of batch BF3 in 0.1N HCL

Table no.10.22

Sr.no	Time (min)	Percent drug release
1	**0**	**1.2**
2	**1**	**17.12**
3	**2**	**22.39**
4	**3**	**33.80**
5	**4**	**39.62**
6	**5**	**43.46**
7	**6**	**58.39**
8	**7**	**64.42**
9	**8**	**67.5**
10	**9**	**79.79**
11	**10**	**87.37**
12	**11**	**88.46**
13	**12**	**99.43**

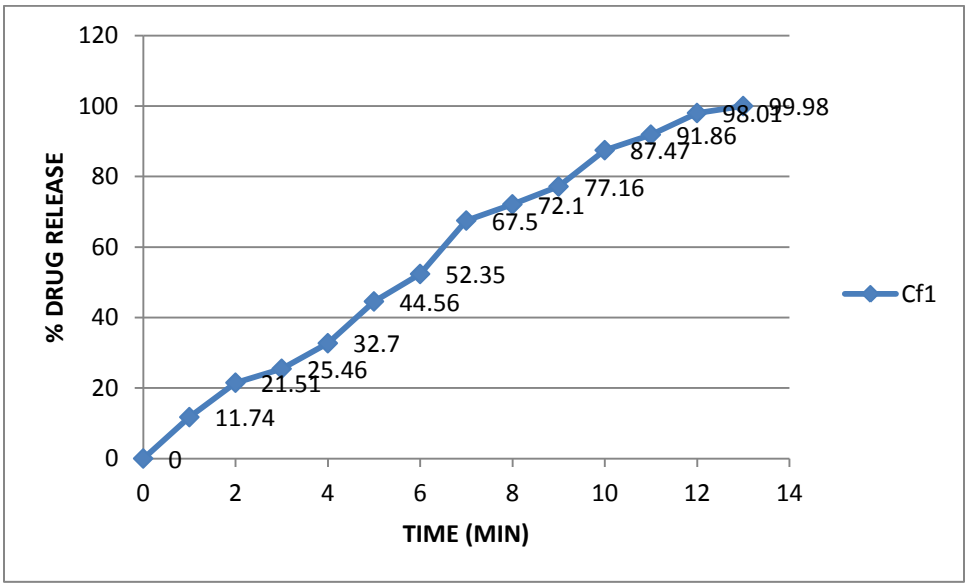


Graph No 10.9 In-vitro release studies of batch BF3 in 0.1N HCL

In-vitro release studies of batchCF1 in 0.1N HCL

Table no.10.23

Sr.no	Time (min)	Percent drug release
1	**0**	**0**
2	**1**	**11.74**
3	**2**	**21.51**
4	**3**	**25.46**
5	**4**	**32.70**
6	**5**	**44.56**
7	**6**	**52.35**
8	**7**	**67.5**
9	**8**	**72.10**
10	**9**	**77.16**
11	**10**	**87.47**
12	**11**	**91.86**
13	**12**	**98.01**
14	**13**	**99.98**

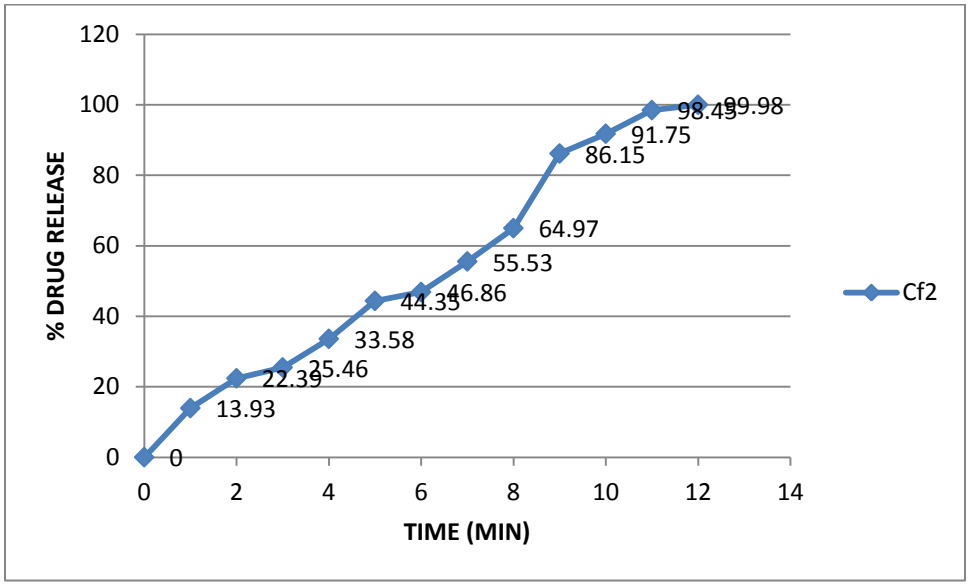


Graph No 10.10 In-vitro release studies of batch CF1 in 0.1N HCL

In-vitro release studies of batch CF2 in 0.1N HCL

Table no.10.24

Sr.no	Time (min)	Percent drug release
1	**0**	**0**
2	**1**	**13.93**
3	**2**	**22.39**
4	**3**	**25.46**
5	**4**	**33.58**
6	**5**	**44.35**
7	**6**	**46.86**
8	**7**	**55.53**
9	**8**	**64.97**
10	**9**	**86.15**
11	**10**	**91.75**
12	**11**	**98.45**
13	**12**	**99.98**

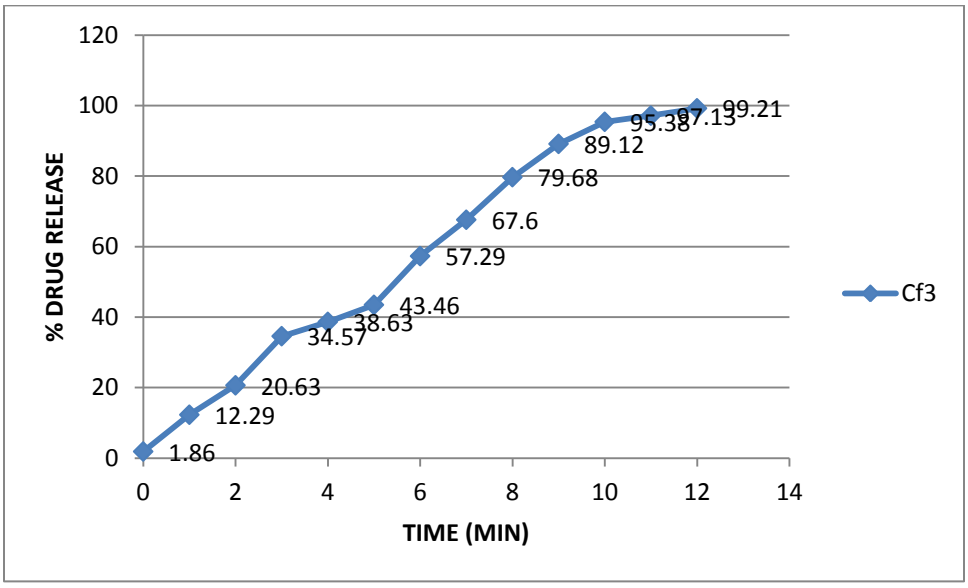


Graph No 10.11 In-vitro release studies of batch CF2in 0.1N HCL

In-vitro release studies of batch CF3 in 0.1N HCL

Table no.10.25

Sr.no	Time (min)	Percent drug release
1	**0**	**1.86**
2	**1**	**12.29**
3	**2**	**20.63**
4	**3**	**34.57**
5	**4**	**38.63**
6	**5**	**43.46**
7	**6**	**57.29**
8	**7**	**67.60**
9	**8**	**79.68**
10	**9**	**89.12**
11	**10**	**95.38**
12	**11**	**97.13**
13	**12**	**99.21**



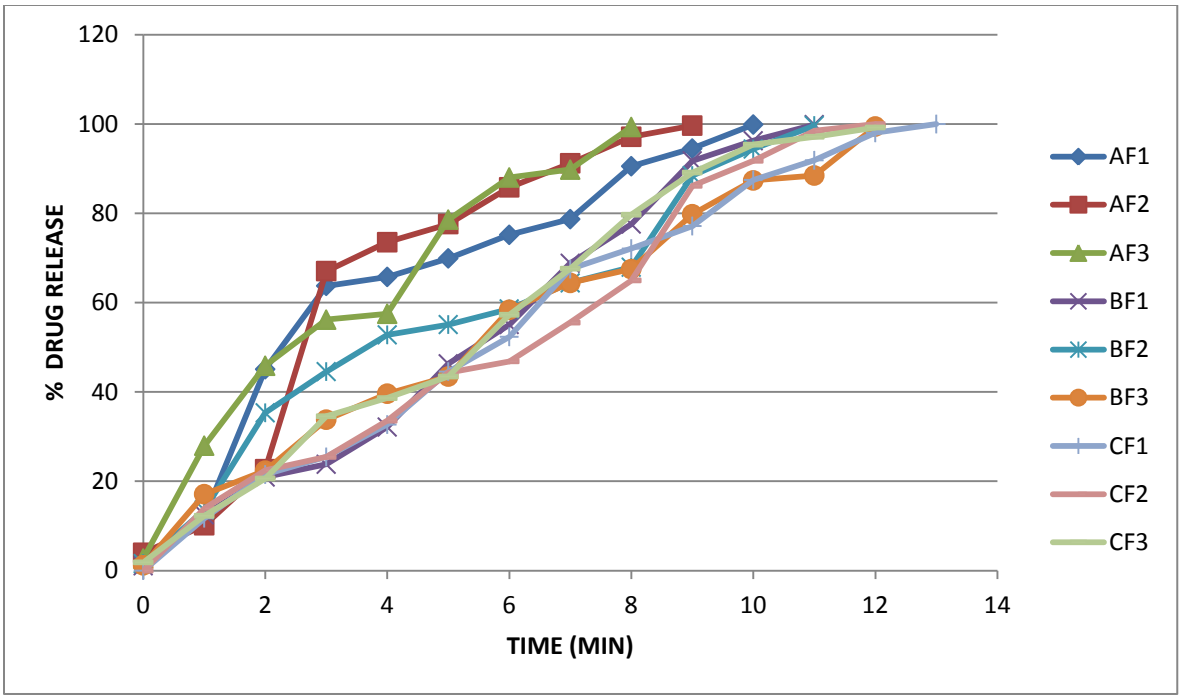
Graph No 10.12 In-vitro release studies of batch CF3 in 0.1N HCL

COMPARATIVE IN VITRO DRUG RELEASE PROFILE OF ORAL DISPERSIBLE TABLET OF CINNARIZINE IN 0.1N HCL

TABLE NO.10.26

Sr. no	Time (min.)	Percent drug release								
		AF1	AF2	AF3	BF1	BF2	BF3	CF1	CF2	CF3
1	0	1.86	4.0	2.7	1.09	1.6	1.2	0	0	1.86
2	1	12.08	10.17	27.98	12.51	13.60	17.12	11.74	13.93	12.29
3	2	45.10	22.71	45.87	20.96	35.34	22.39	21.51	22.46	20.63
4	3	63.76	67.06	56.19	23.81	44.56	33.80	25.46	25.46	34.57
5	4	65.76	73.53	57.52	32.15	52.80	39.62	32.70	33.58	38.63
6	5	69.91	77.59	78.69	46.31	55.09	43.46	44.56	44.35	43.46
7	6	75.18	85.82	88.02	55.09	58..60	58.39	52.35	46.86	57.29
8	7	78.69	91.21	89.78	68.81	64.42	64.42	67.5	55.53	67.60
9	8	90.54	97.13	99.32	77.59	67.93	67.5	72.10	64.97	79.68
10	9	94.5	99.63		91.76	88.46	79.79	77.16	86.15	89.12
11	10	99.87			96.25	94.39	87.37	87.47	91.75	95.38
12	11				99.87	99.65	88.46	91.86	98.45	97.13
13	12						99.43	98.01	99.98	99.21
14	13							99.98		

Form the above observation we can conclude that, as concentration of crospovidone, croscarmellose and cellactose80 increase the disintegration time also increase. But the superdisintegrant crospovidone gives the minimum disintegrating time as compare to croscarmellose or cellactose80. In the batch of crospovidone gives minimum disintegrating time i.e 8 mins and at the concentration of 10% of crospovidone. And the batch of croscarmellose and cellactose80 (at the same conc. Of superdisintegration i.e 10%) gives the disintegration time in the range of 11-12 min and 12-13 min respectively.



Graph No 10.13 COMPARATIVE IN VITRO DRUG RELEASE PROFILE OF ORAL DISPERSIBLE TABLET OF CINNARIZINE IN 0.1N HCL

STABILITY STUDIES OF CINNARIZINE TABLETS

Aging studies of formulation of Oral dispersible tablets of Cinnarizine

40^0c ± 2^0c /75% RH ± 5% RH and At Room Temperature

Table no.10.27. ****≤ No Change**

Sr .no	Evaluation Parameter	Observation
		AF3
1	Physical Appearance	**
2	Weight Variation (mg)	**
3	Hardness(kg/cm^2)	2.00
4	Friability (%)	0.70
5	Drug content(mg/tablet)	98.96

10) SUMMARY AND CONCLUSION

10.1) Summary

Cinnarizine is the antihistamine and widely used for treatment of nausea and vomiting due to motion sickness. Cinnarine act by interfering with signal transmission between vestibular tissue of inner ear and vomiting center of hypothalamus.

Cinnarizine is rapidly absorbed and distributed in GI tract and has peak plasma concentration(1-3hrs) Cinnarizine undergoes number of biotransformation which include N-oxidation, C-oxidation and oxidative cleavage of drug. It undergoes metabolism and has half life(3-4hrs) after oral admistration , so cinnarizine is effective in the control of antihistamine.

The aim of present work was to prepare a suitable oral dispersible tablet of Cinnarizine; twice a day Cinnarizine dosage form could reduce the dosing frequency and improve patient compliance

Croscarmellose sodium, Crospovidone, Cellactose80 are used as superdisintegrants at minimum to maximum quantity which give better disintegration time with better releasing time was studied. The study gives the report that as we increase the concentration of superdisintegrating agents the disintegrating time and in-vitro drug release are also increases

In the study all the formulation were subjected to physical parameters of tablets, like hardness, friability, weight variation, drug content of Cinnarizine. All the formulations resulted in acceptable limit except formulation AF3 and CF2 for hardness test marginally of the tablets. The final batch AF3 can be considered as optimized batch as it seems to be most promising formulation which gives the release up to **99.32**% in 8 min.

The drug-excipients interaction studies were carried out by FTIR. No significant interaction of drug with excipients was observed. During stability studies, no significant variation (1 to 3 %) in drug release was observed, indicating that formulation batch AF3 was stable over the chosen condition for 3 months.

The optimized formulation batch AF3 showed better drug release profile with other formulations.

Conclusion

From the present study carried out on Cinnarizine oraldispersible tablet using by direct compression method, the following conclusion can be drawn.

The total weight of optimized AF3 batch was 200 mg contained Cinnarizine-12.5%, crospovidone-10%, lactose-10%, microcrystalline cellulose-12.5%, magnesium stearate-2.5%, sodium lauryl sulphate-1%, menthol-1%, aspartame-5%, mannitol-45.5%

The Prefromulation study gives the following information of optimize batch Angle of Repose-30.60 good to flow, Bulk density-0.5, Tapped density-0.625, Compressibility Index-15.79 good to flow, Hausner ratio-1.25

Post parameter evaluation of tablets shows the following readings are Weight variation-200.765±, Thickness uniformity-3.558, Hardness-2.02, Friability-0.589, Tensile strength-4.09, Disintegration time-25 sec, Water absorption ratio-, Content uniformity-99.96%, In-vitro release studies- in 9 min. The drug content is to be find out.

A more the concentration of crospovidone is used for quick the disintegration and dissolution is to bee find out. The results give information that Disintegration time in 25 sec. so crospovidone is the optimize batch on basis of disintegration time and in-vitro drug release.

All the formulation batches fulfill the official limit for physical parameters like weight variation, hardness, friability and drug content uniformity. The in-vitro drug release studies indicated that the optimum release profile was found by the formulation batch AF3. By drug-excipients interaction studies, no significant interaction was found. Formulation batch AF3 was found to be stable over the chosen temperature and humidity for 3 months.

The optimized formulation of batch Af3 gave the best vitro release of 99.32% in 8min in 0.1N HCL. The release of drug followed matrix diffusion mechanism.

Our objective to fast dispersion of the tablet in oral cavity in quick time and has fulfilled and it definately gives the fast release action for its histamine activity. The oral dispersible tablets gives the quick onset of action as compared to convectional dosage form

leading to facilitation of its quick activity at the minimum time period. Hence it can be concluded that the formulation AF3 is a stable and effective for quick action.

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